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ANESTHESIA & ANALGESIA

Journal of the International Anesthesia Research Society

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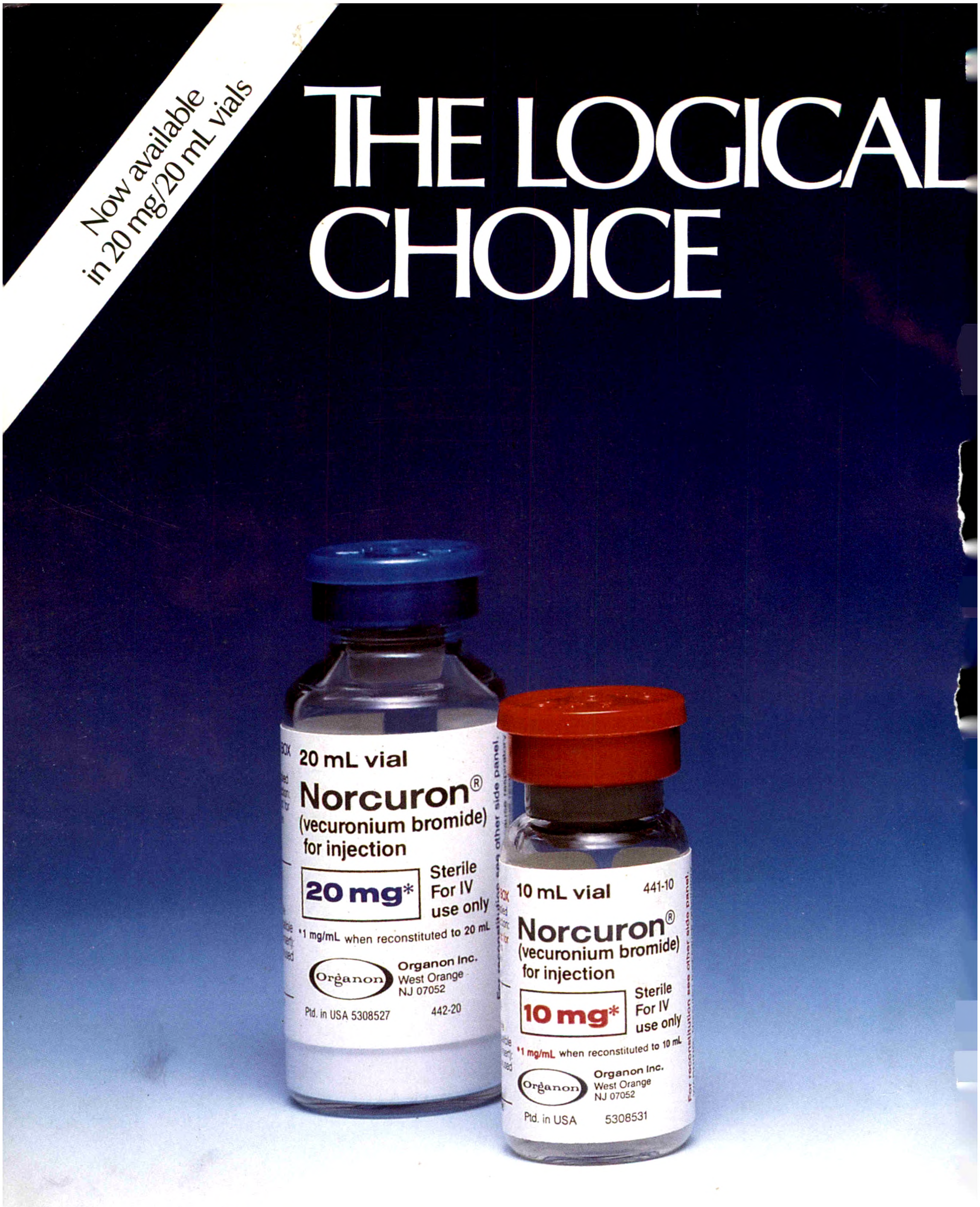
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Vol. 75

CRUCIAL PARAMETERS IN SELECTING A NEUROMUSCULAR BLOCKING AGENT

	Norcuron® (vecuronium bromide) for injection	Atracurium besylate
HEMODYNAMICS	No significant variations in blood pressure, cardiac output, or systemic vascular resistance.[1]	Statistically significant variations in blood pressure, cardiac output, and systemic vascular resistance.[1] ($P<.05$)
HISTAMINE	Available clinical experience indicates that reactions commonly associated with histamine release are unlikely to occur.[1-4]	Precautions advised for patients in whom substantial histamine release would be hazardous (eg, clinically significant cardiovascular disease, asthma).[5]
RECOVERY To 25% of control To 95% of control	 25-40 min[3] 45-65 min[3]	 35-45 min[5] 60-70 min[5]
DOSING FLEXIBILITY	The initial recommended dose is 0.08-0.1 mg/kg. Dose can be increased up to 0.28 mg/kg for long cases without significant histamine release or related cardiovascular side effects.[1,3,4]	Initial recommended dose is 0.4-0.5 mg/kg. A moderate histamine release and significant falls in blood pressure have been seen following a dose of 0.5 mg/kg ($P<.05$) and 0.6 mg/kg.[*2,5,6]
STORAGE & SHELF LIFE	2-year shelf life in lyophilized form at room temperature.† Can be reconstituted with various IV solutions including Lactated Ringers.‡	2-year shelf life under constant refrigeration.† Upon removal from refrigeration to room temperature storage, use within 14 days even if rerefrigerated.[5]

* Dose of atracurium above 0.5 mg/kg is not recommended.
† As originally supplied by the respective manufacturers.
‡ Storage after reconstitution varies with solution. See package insert.

Norcuron®

(vecuronium bromide) for injection

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THE LOGICAL CHOICE FOR NEUROMUSCULAR BLOCKADE

See following page for brief summary of prescribing information.

Organon
ORGANON INC.
WEST ORANGE
NEW JERSEY 07052

Norcuron®

(vecuronium bromide) for injection

Before prescribing, please consult complete product information, a summary of which follows:

THIS DRUG SHOULD BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS.

CONTRAINDICATIONS: Norcuron® is contraindicated in patients known to have a hypersensitivity to it.

WARNINGS: NORCURON® SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION. TO REDUCE THE POSSIBILITY OF PROLONGED NEUROMUSCULAR BLOCKADE AND OTHER POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING LONG-TERM USE IN THE ICU, NORCURON® OR ANY OTHER NEUROMUSCULAR BLOCKING AGENT SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSES BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH ITS ACTIONS AND WHO ARE FAMILIAR WITH APPROPRIATE PERIPHERAL NERVE STIMULATOR MUSCLE MONITORING TECHNIQUES (see PRECAUTIONS). In patients who are known to have myasthenia gravis or the myasthenic (Eaton-Lambert) syndrome, small doses of Norcuron® may have profound effects. In such patients, a peripheral nerve stimulator and use of a small test dose may be of value in monitoring the response to administration of muscle relaxants.

PRECAUTIONS:

Renal Failure: Norcuron® is well tolerated without clinically significant prolongation of neuromuscular blocking effect in patients with renal failure who have been optimally prepared for surgery by dialysis. Under emergency conditions in anephric patients some prolongation of neuromuscular blockage may occur; therefore, if anephric patients cannot be prepared for non-elective surgery, a lower initial dose of Norcuron® should be considered.

Altered Circulation Time: Conditions associated with slower circulation time in cardiovascular disease, old age, edematous states resulting in increased volume of distribution may contribute to a delay in onset time, therefore dosage should not be increased.

Hepatic Disease: Limited experience in patients with cirrhosis or cholestasis has revealed prolonged recovery time in keeping with the role the liver plays in Norcuron® metabolism and excretion. Data currently available do not permit dosage recommendations in patients with impaired liver function.

Long-term Use in I.C.U.: In the intensive care unit, in rare cases, long-term use of neuromuscular blocking drugs to facilitate mechanical ventilation may be associated with prolonged paralysis and/or skeletal muscle weakness that may be first noted during attempts to wean such patients from the ventilator. Typically, such patients receive other drugs such as broad spectrum antibiotics, narcotics and/or steroids and may have electrolyte imbalance and diseases which lead to electrolyte imbalance, hypoxic episodes of varying duration, acid-base imbalance and extreme debilitation, any of which may enhance the actions of a neuromuscular blocking agent. Additionally, patients immobilized for extended periods frequently develop symptoms consistent with disuse muscle atrophy. The recovery picture may vary from regaining movement and strength in all muscles to initial recovery of movement of the facial and small muscles of the extremities then to the remaining muscles. In rare cases recovery may be over an extended period of time and may even, on occasion, involve rehabilitation. Therefore, when there is a need for long-term mechanical ventilation, the benefits-to-risk ratio of neuromuscular blockade must be considered. Continuous infusion or intermittent bolus dosing to support mechanical ventilation has not been studied sufficiently to support dosage recommendations.

IN THE INTENSIVE CARE UNIT, APPROPRIATE MONITORING, WITH THE USE OF A PERIPHERAL NERVE STIMULATOR TO ASSESS THE DEGREE OF NEUROMUSCULAR BLOCKADE IS RECOMMENDED TO HELP PRECLUDE POSSIBLE PROLONGATION OF THE BLOCKADE. WHENEVER THE USE OF NORCURON® OR ANY NEUROMUSCULAR BLOCKING AGENT IS CONTEMPLATED IN THE ICU, IT IS RECOMMENDED THAT NEUROMUSCULAR TRANSMISSION BE MONITORED CONTINUOUSLY DURING ADMINISTRATION AND RECOVERY WITH THE HELP OF A NERVE STIMULATOR. ADDITIONAL DOSES OF NORCURON® OR ANY OTHER NEUROMUSCULAR BLOCKING AGENT SHOULD NOT BE GIVEN BEFORE THERE IS A DEFINITE RESPONSE TO T_1 OR TO THE FIRST TWITCH. IF NO RESPONSE IS ELICITED, INFUSION ADMINISTRATION SHOULD BE DISCONTINUED UNTIL A RESPONSE RETURNS.

Severe Obesity or Neuromuscular Disease: Patients with severe obesity or neuromuscular disease may pose airway and/or ventilatory problems requiring special care before, during and after the use of neuromuscular blocking agents such as Norcuron®.

Malignant Hyperthermia: Many drugs used in anesthetic practice are suspected of being capable of triggering a potentially fatal hypermetabolism of skeletal muscle known as malignant hyperthermia. There are insufficient data derived from screening in susceptible animals (swine) to establish whether or not Norcuron® is capable of triggering malignant hyperthermia.

C.N.S.: Norcuron® has no known effect on consciousness, the pain threshold or cerebration. Administration must be accompanied by adequate anesthesia or sedation.

Drug Interactions: Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron® (vecuronium bromide) for injection and its duration of action. If succinylcholine is used before Norcuron®, the administration of Norcuron® should be delayed until the succinylcholine effect shows signs of wearing off. With succinylcholine as the intubating agent, initial doses of 0.04-0.06 mg/kg of Norcuron® may be administered to produce complete neuromuscular block with clinical duration of action of 25-30 minutes. The use of Norcuron® before succinylcholine, in order to attenuate some of the side effects of succinylcholine, has not been sufficiently studied.

Other nondepolarizing neuromuscular blocking agents (pancuronium, d-tubocurarine, metocurine, and gallamine) act in the same fashion as does Norcuron®, therefore these drugs and Norcuron® may manifest an additive effect when used together. There are insufficient data to support concomitant use of Norcuron® and other competitive muscle relaxants in the same patient.

Inhalational Anesthetics: Use of volatile inhalational anesthetics such as enflurane, isoflurane, and halothane with Norcuron® will enhance neuromuscular blockade. Potentiation is most prominent with use of enflurane and isoflurane. With the above agents the initial dose of Norcuron® may be the same as with balanced anesthesia unless the inhalational anesthetic has been administered for a sufficient time at a sufficient dose to have reached clinical equilibrium.

Antibiotics: Parenteral/intraperitoneal administration of high doses of certain antibiotics may intensify or produce neuromuscular block on their own. The following antibiotics have been associated with various degrees of paralysis: aminoglycosides (such as neomycin, streptomycin, kanamycin, gentamicin, and dihydrostreptomycin); tetracyclines; bacitracin; polymyxin B; colistin; and sodium colistimethate. If these or other newly introduced antibiotics are used in conjunction with Norcuron®, unexpected prolongation of neuromuscular block should be considered a possibility.

Other: Experience concerning injection of quinidine during recovery from use of other muscle relaxants suggest that recurrent paralysis may occur. This possibility must also be considered for Norcuron®. Norcuron® induced neuromuscular blockade has been counteracted by alkalosis and enhanced by acidosis in experimental animals (cat). Electrolyte imbalance and diseases which lead to electrolyte imbalance, such as adrenal cortical insufficiency, have been shown to alter neuromuscular blockade. Depending on the nature of the imbalance, either enhancement or inhibition may be expected. Magnesium salts, administered for the management of toxemia of pregnancy, may enhance the neuromuscular blockade.

Drug/laboratory test interactions: None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential or impairment of fertility.

Pregnancy: Pregnancy Category C: Animal reproduction studies have not been conducted with Norcuron®. It is also not known whether Norcuron® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Norcuron® should be given to a pregnant woman only if clearly needed.

Pediatric Use: Infants under 1 year of age but older than 7 weeks, also tested under halothane anesthesia, are moderately more sensitive to Norcuron® on a mg/kg basis than adults and take about 1½ times as long to recover. Information presently available does not permit recommendations for usage in neonates.

ADVERSE REACTIONS: The most frequent adverse reaction to nondepolarizing blocking agents as a class consists of an extension of the drug's pharmacological action beyond the time period needed. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiration insufficiency or apnea.

Inadequate reversal of the neuromuscular blockade is possible with Norcuron® as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate. Little or no increase in intensity of blockade or duration of action with Norcuron® is noted from the use of thiobarbiturates, narcotic analgesics, nitrous oxide, or droperidol. See OVERDOSAGE for discussion of other drugs used in anesthetic practice which also cause respiratory depression.

Prolonged to profound extensions of paralysis and/or muscle weakness as well as muscle atrophy have been reported after long-term use to support mechanical ventilation in the intensive care unit (see PRECAUTIONS).

The administration of Norcuron® has been associated with rare instances of hypersensitivity reactions (bronchospasm, hypotension and/or tachycardia, sometimes associated with acute urticaria or erythema).

OVERDOSAGE: The possibility of iatrogenic overdosage can be minimized by carefully monitoring muscle twitch response to peripheral nerve stimulation.

Excessive doses of Norcuron® produce enhanced pharmacological effects. Residual neuromuscular blockage beyond the time period needed may occur with Norcuron® as with other neuromuscular blockers. This may be manifested by skeletal muscle weakness, decreased respiratory reserve, low tidal volume, or apnea. A peripheral nerve stimulator may be used to assess the degree of residual neuromuscular blockade from other causes of decreased respiratory reserve.

Respiratory depression may be due either wholly or in part to other drugs used during the conduct of general anesthesia such as narcotics, thiobarbiturates and other central nervous system depressants. Under such circumstances, the primary treatment is maintenance of a patent airway and manual or mechanical ventilation until complete recovery of normal respiration is assured. Regonol® (pyridostigmine bromide) injection, neostigmine, or edrophonium, in conjunction with atropine or glycopyrrolate will usually antagonize the skeletal muscle relaxant action of Norcuron®. Satisfactory reversal can be judged by adequacy of skeletal muscle tone and by adequacy of respiration. A peripheral nerve stimulator may also be used to monitor restoration of

of prolonged neuromuscular blockade. Ventilation must be supported by artificial means until the patient has resumed cor of his respiration. Prior to the use of reversal agents, reference should be made to the specific package insert of the reversal age

DOSAGE AND ADMINISTRATION: Before prescribing, please consult complete product information. Norcuron® (vecuronium bromide) for injection is for intravenous use only. This drug should be administered by or under the supervision experienced clinicians familiar with the use of neuromuscular blocking agents. Dosage must be individualized in each cas dosage information which follows is derived from studies based upon units of drug per unit of body weight and is intende serve as a guide only, especially regarding enhancement of neuromuscular blockade of Norcuron® by volatile anesthetics by prior use of succinylcholine (see PRECAUTIONS/Drug Interactions). Parenteral drug products should be inspected vis for particulate matter and discoloration prior to administration whenever solution and container permit.

To obtain maximum clinical benefits of Norcuron® and to minimize the possibility of overdosage, the monitoring of mu twitch response to peripheral nerve stimulation is advised.

The recommended initial dose of Norcuron® is 0.08 to 0.10 mg/kg (1.4 to 1.75 times the ED_{90}) given as an intravenous injection. This dose can be expected to produce good or excellent non-emergency intubation conditions in 2.5 to 3 minu after injection. Under balanced anesthesia, clinically required neuromuscular blockade lasts approximately 25-30 minutes recovery to 25% of control achieved approximately 25 to 40 minutes after injection and recovery to 95% of control achie approximately 45-65 minutes after injection. In the presence of potent inhalation anesthetics, the neuromuscular block of Norcuron® is enhanced. If Norcuron® is first administered more than 5 minutes after the start of inhalation agent or steady state has been achieved, the initial Norcuron® dose may be reduced by approximately 15%, i.e., 0.060 to 0.08

Prior administration of succinylcholine may enhance the neuromuscular blocking effect and duration of action of N If intubation is performed using succinylcholine, a reduction of initial dose of Norcuron® to 0.04-0.06 mg/kg with inh anesthesia and 0.05-0.06 mg/kg with balanced anesthesia may be required.

During prolonged surgical procedures, maintenance doses of 0.010 to 0.015 mg/kg of Norcuron® are recommende initial Norcuron® injection, the first maintenance dose will generally be required within 25 to 40 minutes. However, cli ria should be used to determine the need for maintenance doses. Since Norcuron® lacks clinically important cumulati subsequent maintenance doses, if required, may be administered at relatively regular intervals for each patient, ranging imately from 12 to 15 minutes under balanced anesthesia, slightly longer under inhalation agents. (If less frequent adm tion is desired, higher maintenance doses may be administered.)

Should there be reason for the selection of larger doses in individual patients, initial doses ranging from 0.15 mg/kg 0.28 mg/kg have been administered during surgery under halothane anesthesia without ill effects to the cardiovascular s being noted as long as ventilation is properly maintained.

Use by Continuous Infusion: After an intubating dose of 80-100 μg/kg, a continuous infusion of 1 μg/kg/min can be i ated approximately 20-40 min later. Infusion of Norcuron® should be initiated only after early evidence of spontaneous rec from the bolus dose. Long-term intravenous infusion to support mechanical ventilation in the intensive care unit has not be studied sufficiently to support dosage recommendations (see PRECAUTIONS).

The infusion of Norcuron® should be individualized for each patient. The rate of administration should be adjusted acc to the patient's twitch response as determined by peripheral nerve stimulation. An initial rate of 1 μg/kg/min is recommen with the rate of the infusion adjusted thereafter to maintain a 90% suppression of twitch response. Average infusion rates range from 0.8 to 1.2 μg/kg/min.

Inhalation anesthetics, particularly enflurane and isoflurane may enhance the neuromuscular blocking action of non-depolarizing muscle relaxants. In the presence of steady-state concentrations of enflurane or isoflurane, it may be necessa reduce the rate of infusion 25-60 percent, 45-60 min after the intubating dose. Under halothane anesthesia it may not be essary to reduce the rate of infusion.

Spontaneous recovery and reversal of neuromuscular blockade following discontinuation of Norcuron® infusion may be expected to proceed at rates comparable to that following a single bolus dose.

Infusion solutions of Norcuron® can be prepared by mixing Norcuron® with an appropriate infusion solution such as 5 glucose in water, 0.9% NaCl, 5% glucose in saline, or Lactated Ringers. Unused portions of infusion solutions should be discarded.

Infusion rates of Norcuron® can be individualized for each patient using the following table:

Drug Delivery Rate (μg/kg/min)	Infusion Delivery Rate (mL/kg/min)	
	0.1 mg/mL*	0.2 mg/mL†
0.7	0.007	0.0035
0.8	0.008	0.0040
0.9	0.009	0.0045
1.0	0.010	0.0050
1.1	0.011	0.0055
1.2	0.012	0.0060
1.3	0.013	0.0065

*10 mg of Norcuron® in 100 mL solution †20 mg of Norcuron® in 100 mL solution

The following table is a guideline for mL/min delivery for a solution of 0.1 mg/mL (10 mg in 100 mL) with an infusion pum

NORCURON® INFUSION RATE – mL/MIN

Amount of Drug μg/kg/min	Patient Weight – kg						
	40	50	60	70	80	90	1
0.7	0.28	0.35	0.42	0.49	0.56	0.63	(
0.8	0.32	0.40	0.48	0.56	0.64	0.72	0.
0.9	0.36	0.45	0.54	0.63	0.72	0.81	0.
1.0	0.40	0.50	0.60	0.70	0.80	0.90	1.
1.1	0.44	0.55	0.66	0.77	0.88	0.99	1
1.2	0.48	0.60	0.72	0.84	0.96	1.08	1
1.3	0.52	0.65	0.78	0.91	1.04	1.17	

NOTE: If a concentration of 0.2 mg/mL is used (20 mg in 100 mL), the rate should be decreased by one-half.

Dosage in Children: Older children (10 to 17 years of age) have approximately the same dosage requirements (mg adults and may be managed the same way. Younger children (1 to 10 years of age) may require a slightly higher initial may also require supplementation slightly more often than adults. Infants under one year of age but older than 7 week moderately more sensitive to Norcuron® on a mg/kg basis than adults and take about 1½ times as long to recover. See subsection of PRECAUTIONS titled Pediatric Use. Information presently available does not permit recommendation on neonates (see PRECAUTIONS). There are insufficient data concerning continuous infusion of vecuronium in children, th no dosing recommendation can be made.

COMPATIBILITY: Norcuron® is compatible in solution with:

0.9% NaCl solution	Sterile water for injection	Lactated Ringers
5% glucose in water	5% glucose in saline	

Use within 24 hours of mixing with the above solutions.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administratio ever solution and container permit.

HOW SUPPLIED:

10 mL vials (10 mg vecuronium bromide) and 10 mL prefilled syringes of diluent (bacteriostatic water for injection, US 22 g 1¼" needle. Boxes of 10 NDC No. 0052-0441-60

10 mL vials (10 mg vecuronium bromide) and 10 mL vials of diluent (bacteriostatic water for injection, USP). Boxes of 10 NDC No. 0052-0441-17

10 mL vials (10 mg vecuronium bromide) only; DILUENT NOT SUPPLIED. Boxes of 10 NDC No. 0052-0441

20 mL vials (20 mg vecuronium bromide) only; DILUENT NOT SUPPLIED. Boxes of 10 NDC No. 0052-044

STORAGE: 15°-30°C (59°-86°F). Protect from light.

AFTER RECONSTITUTION:

- When reconstituted with supplied bacteriostatic water for injection: CONTAINS BENZYL ALCOHOL, WHICH IS NOT INTENDED FOR USE IN NEWBORNS. Use within 5 days. May be stored at room temperature or refrigerated.
- When reconstituted with sterile water for injection or other compatible I.V. solutions: Refrigerate vial. Use within 24 Single use only. Discard unused portion.

Caution: Federal law prohibits dispensing without prescription. REVIS

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*Tracrium is a registered trademark of Burroughs Wellcome Co.

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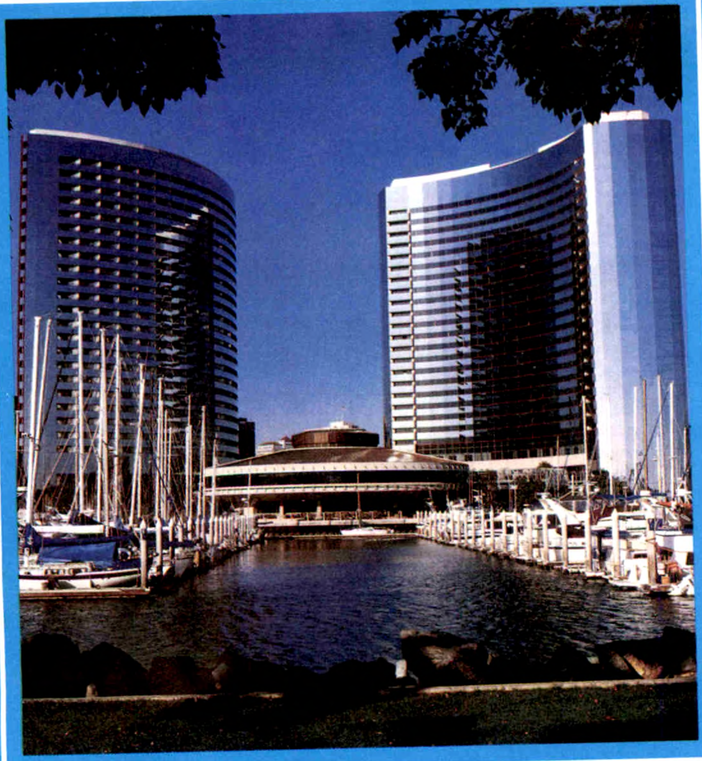

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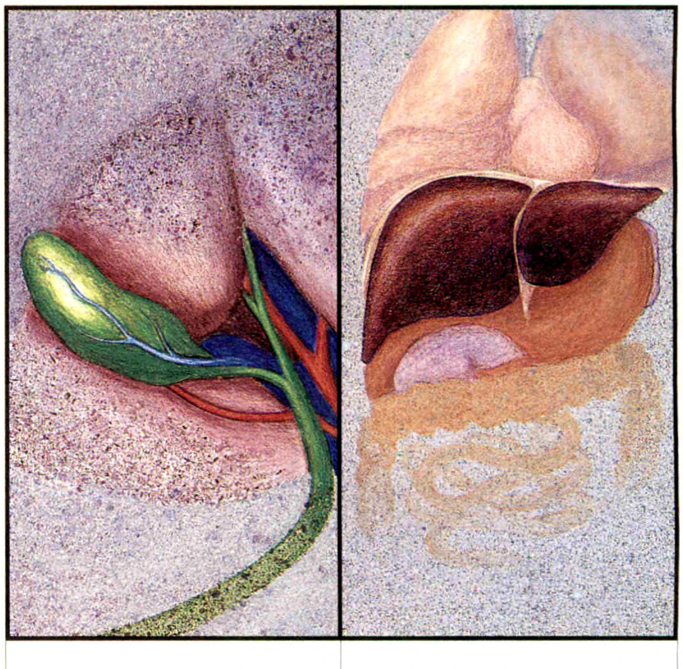

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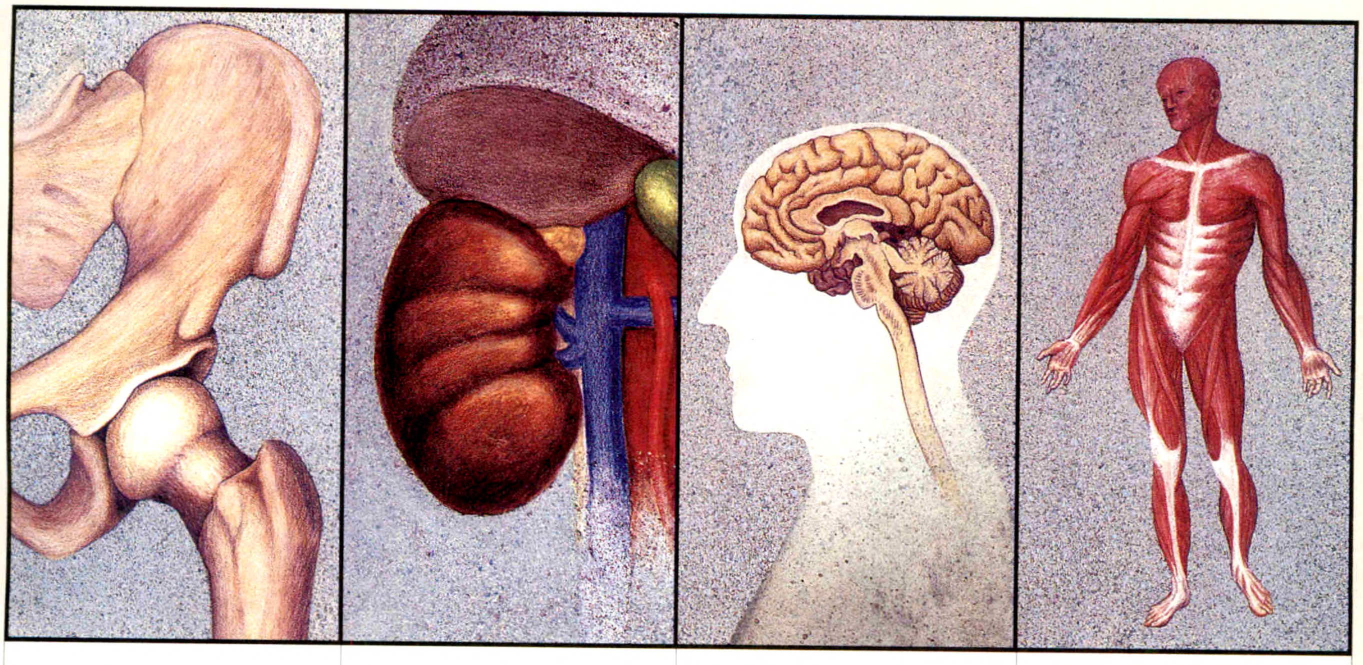

Total hip replacement	**Renal surgery**	**Neurosurgery for trauma**	**Everyday procedures**
Common patient type Elderly women and men	**Common patient type** Both adults and children	**Common patient type** Both adults and children	**Common patient type** Average
Advantage of Tracrium Recovery time unaffected by age.[3]	**Advantage of Tracrium** Recovery time unaffected by renal dysfunction.[2]	**Advantage of Tracrium** Effect unchanged by concomitant anticonvulsant medications (phenytoin, carbamazepine).[4,5]	**Advantage of Tracrium** The same reasons Tracrium is ideal for special patient types make it the choice for everyday procedures.

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PRECAUTIONS: General: Although Tracrium is a less potent histamine releaser than d-tubocurarine or metocurine, the possibility of substantial histamine release in sensitive individuals must be considered. Special caution should be exercised in administering Tracrium to patients in whom substantial histamine release would be especially hazardous (e.g., patients with clinically significant cardiovascular disease) and in patients with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release. In these patients, the recommended initial Tracrium dose is lower (0.3 to 0.4 mg/kg) than for other patients and should be administered slowly or in divided doses over one minute. Since Tracrium has no clinically significant effects on heart rate in the recommended dosage range, it will not counteract the bradycardia produced by many anesthetic agents or vagal stimulation. As a result, bradycardia during anesthesia may be more common with Tracrium than with other muscle relaxants. Tracrium may have profound effects in patients with myasthenia gravis, Eaton-Lambert syndrome, or other neuromuscular diseases in which potentiation of nondepolarizing agents has been noted. The use of a peripheral nerve stimulator is especially important for assessing neuromuscular blockade in these patients. Similar precautions should be taken in patients with severe electrolyte disorders or carcinomatosis. Multiple factors in anesthesia practice are suspected of triggering malignant hyperthermia (MH), a potentially fatal hypermetabolic state of skeletal muscle. Halogenated anesthetic agents and succinylcholine are recognized as the principal pharmacologic triggering agents in MH-susceptible patients; however, since MH can develop in the absence of established triggering agents, the clinician should be prepared to recognize and treat MH in any patient scheduled for general anesthesia. Reports of MH have been rare in cases in which Tracrium has been used. In studies of MH-susceptible animals (swine) and in a clinical study of MH-susceptible patients, Tracrium did not trigger this syndrome. Resistance to nondepolarizing neuromuscular blocking agents may develop in burn patients. Increased doses of nondepolarizing muscle relaxants may be required in burn patients and are dependent on the time elapsed since the burn injury and the size of the burn. The safety of Tracrium has not been established in patients with bronchial asthma. **Long-Term Use in Intensive Care Unit (ICU):** Tracrium has been used to facilitate mechanical ventilation in ICU patients. When there is a need for long-term mechanical ventilation, the benefits to risk ratio of neuromuscular blockade must be considered. There is only limited information on the efficacy and safety of Tracrium administered by long-term (days to weeks) intravenous infusion to facilitate mechanical ventilation in intensive care facilities. For Tracrium, as with other neuromuscular blocking agents used in intensive care facilities, available evidence suggests that there is wide interpatient variability in dosage requirements and that these requirements may change with time. Limited data suggest that Tracrium infusion requirements may increase with prolonged administration in the ICU. As with other neuromuscular blocking agents, little information is available on the plasma levels or clinical consequences of atracurium metabolites following long-term (days to weeks) infusion of Tracrium in the intensive care unit setting. One metabolite of atracurium, laudanosine, when administered alone to laboratory animals, has been associated with cerebral excitatory effects. Physiological effects of laudanosine in humans have not been demonstrated. The effects of hemodialysis, hemoperfusion and hemofiltration on plasma levels of atracurium and its metabolites are unknown. **Drug Interactions:** Drugs which may enhance neuromuscular blocking action of Tracrium include: enflurane; isoflurane; halothane; certain antibiotics, especially the aminoglycosides and polymyxins; lithium; magnesium salts; procainamide; and quinidine. If other muscle relaxants are used during the same procedure, the possibility of a synergistic or antagonist effect should be considered. The prior administration of succinylcholine does not enhance the duration, but quickens the onset and may increase the depth, of neuromuscular blockade induced by Tracrium. Tracrium should not be administered until a patient has recovered from succinylcholine-induced neuromuscular blockade. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** A positive response was observed in the mouse lymphoma assay under conditions which killed over 80% of the treated cells. A far weaker response was observed in the presence of metabolic activation at concentrations which also killed over 80% of the treated cells. **Pregnancy: *Teratogenic Effects:*** Pregnancy Category C. Tracrium has been shown to be potentially teratogenic in rabbits, when given in doses up to approximately one-half the human dose. There are no adequate and well-controlled studies in pregnant women. Tracrium should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Labor and Delivery:** It is not known whether muscle relaxants administered during vaginal delivery have immediate or delayed adverse effects on the fetus or increase the likelihood that resuscitation of the newborn will be necessary. The possibility that forceps delivery will be necessary may increase. Tracrium (0.3 mg/kg) has been administered to 26 pregnant women during delivery by cesarean section. No harmful effects were attributable to Tracrium in any of the newborn infants, although small amounts of Tracrium were shown to cross the placental barrier. The possibility of respiratory depression in the newborn infant should always be considered following cesarean section during which a neuromuscular blocking agent has been administered. In patients receiving magnesium sulfate, the reversal of neuromuscular blockade may be unsatisfactory and Tracrium dose should be lowered as indicated. **Nursing Mothers:** It is not known whether this drug is excreted in human milk. Caution should be exercised when Tracrium is administered to a nursing woman. **Pediatric Use:** Safety and effectiveness in children below the age of 1 month have not been established.

ADVERSE REACTIONS: Observed in Controlled Clinical Studies: Tracrium produced few adverse reactions during extensive clinical trials. Most were suggestive of histamine release (see Precautions Section). The overall incidence rate for clinically important adverse reactions was 7/875 or 0.8%. Most adverse reactions were of little clinical significance unless they were associated with significant hemodynamic changes. Substantial vital sign changes greater than or equal to 30% observed in 530 patients, without cardiovascular disease, were as follows: in those patients given the recommended initial dosage range of 0.31 to 0.50 mg/kg of Tracrium, mean arterial pressure increased in 2.8% and decreased in 2.1% of patients while the heart rate increased in 2.8% of these patients. At doses of ≥ 0.60 mg/kg, 14.3% of the studied patients had a decrease in mean arterial pressure while 4.8% had an increase in heart rate. At doses ≤ 0.30 mg/kg, mean arterial pressure increased in 1.9% and decreased in 1.1% of patients, while heart rate increased in 1.6% and decreased in 0.8% of these patients. **Observed in Clinical Practice:** Based on clinical experience in the U.S. and the United Kingdom of approximately 3 million patients given Tracrium the following adverse reactions are among the most frequently reported: *General:* allergic reactions (anaphylactic or anaphylactoid) which, in rare instances, were severe (e.g., cardiac arrest); *Musculoskeletal:* inadequate, prolonged block; *Cardiovascular:* hypotension, vasodilatation (flushing), tachycardia, bradycardia; *Respiratory:* dyspnea, bronchospasm, laryngospasm; *Integumentary:* rash, urticaria, injection site reaction.

STORAGE: Tracrium Injection should be refrigerated at 2° to 8° C (36° to 46° F) to preserve potency. DO NOT FREEZE. Upon removal from refrigeration to room temperature storage conditions (25° C/77° F), use Tracrium Injection within 14 days even if rerefrigerated.

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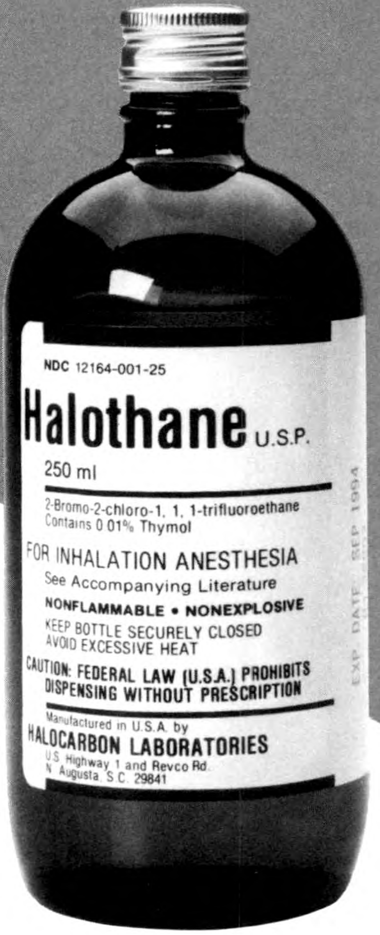
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EDITORIAL

Pharmacology of Hemostasis in the Surgical Patient

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In this issue of *Anesthesia & Analgesia*, Guay et al. (1) report the failure of desmopressin administration to decrease the volume of blood lost or units of blood transfused in patients undergoing spinal fusion for idiopathic scoliosis. The 1986 report by Salzman et al. (2) that desmopressin administration significantly improved hemostasis and decreased blood loss in patients undergoing cardiac surgery associated with large blood loss generated considerable interest in the pharmacology of hemostasis. Subsequent desmopressin studies of similar quality and magnitude in both cardiac and noncardiac surgery have yielded conflicting results (3–5). Does the current report further refute the Salzman study? More properly, the question is, where is desmopressin therapy most likely to be beneficial?

Originally developed for use in the treatment of patients with diabetes insipidus, desmopressin is a synthetic polypeptide analogue of the antidiuretic hormone vasopressin but lacks the vasoconstrictor properties of the latter. Independent observations by Cash et al. (6) and Mannucci et al. (7) that desmopressin increases Factor VIII:C and Factor VIII:vWF concentrations in normal volunteers introduced a new indication for this drug, an indication that today greatly exceeds its original use. Of note, adrenalin, insulin, vasopressin, and nicotine are also capable of increasing the concentration of Factor VIII:C, but undesirable side effects preclude their clinical use for this purpose.

The rapid increase in Factor VIII:C and Factor VIII:vWF concentrations after desmopressin administration suggests that it induces a brisk release of preformed proteins from endogenous stores rather than synthesis of new factors. The observation of progressively poorer responses after repeated administrations (tachyphylaxis) supports this suggestion. Desmopressin has decreased bleeding time or blood loss, or both, in a wide variety of nonspecific conditions, including uremia, Factor IX deficiency, cirrhosis, and platelet dysfunction induced by some drugs. However, desmopressin has proved ineffective in other conditions, such as Glanzmann's thrombasthenia, storage pool deficiency, and thrombocytopenia (8).

It appears that desmopressin is most likely (but not always) to have a beneficial effect where some preexisting condition exists. The Salzman study suggests specifically that a low "normal" Factor VIII:vWF starting level, a cardiopulmonary bypass time >2 h, and an average blood loss >2 L are such conditions (2). This indeed is a very specific, small population of patients in our experience, because few of our patients (including those with aspirin ingestion up to the time of surgery) will lose >2 L of blood without desmopressin administration. Perhaps the inclusion of reoperation answers the question but then further limits the population in whom desmopressin will be effective. Similarly, others have concluded that when applied to a more general population of cardiac surgical patients, desmopressin cannot be shown to have this effect (3,4). The results of Guay et al. (1) similarly identify a subset of patients with scoliosis who are not benefitted by desmopressin. It is clear that desmopressin is unlikely to be beneficial simply because the surgical procedures are associated with large blood losses or procedurally induced platelet dysfunction. More work needs to be done to identify more clearly the patients who will benefit from this drug. Ideally, a test to identify these patients should be developed. It most certainly can be concluded that desmopressin should not become part of a "shotgun approach" in the treatment of excessive bleeding associated with any operative procedure.

The results of this study and others clearly point out that there is no pharmacologic substitute for the three essentials in the hemostatic management of every surgical patient:

1. *A properly taken history and thorough physical examination are the best means of detecting a hemorrhagic diathesis*, be it congenital or acquired. Seeking a patient's hemostatic response to any previous surgical experience is often overlooked in taking the history.

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2. *A screening hemostatic laboratory profile on any patient whose history and physical examination suggest a possible problem with hemostasis.* Additionally, in surgical procedures where there is the potential for large blood loss, such as cardiac surgery and spinal fusion, such a profile will alert physicians to potential problem patients as well as provide a baseline set of tests for comparison should excessive bleeding intraoperatively require additional tests.
3. *Meticulous surgical hemostasis,* without which no amount of questioning, testing, pharmacology, or blood products can provide effective hemostasis.

Finally, in comparing apparently conflicting reports of efficacy in improving hemostasis, the volume of blood transfused may be the most accurate and clinically important measurement of efficacy. Although morbidity may be associated with any significant bleeding, it is entirely another level of concern when the blood lost requires transfusion of homologous blood products. Estimates of intraoperative blood loss are notoriously inaccurate, and only in the case of postoperative losses collected in containers (e.g., chest tube drainage) is accuracy achieved consistently. In evaluating conflicting reports, one must keep in mind that the size of the study population needed to establish a statistical difference is greater for blood transfusion than for blood loss. Groups of patients who start with the same hemoglobin and are transfused to maintain the same target hemoglobin will show a statistically significant difference if the drug or regimen being studied is effective (5). Today, "the current re-emphasis on transmission of viral disease via transfusion suggests . . . clinically important bleeding must include any need for transfusion" (9).

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Adenosine for Controlled Hypotension: Systemic Comparec With Intracoronary Infusion in Dogs

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We hypothesized that either through local myocardial or systemic effects, adenosine could be used to control hypotension during ischemia. Therefore, we compared the effects of systemic with intracoronary infusion of adenosine on myocardial hemodynamics and metabolism during ischemia in 27 dogs. Left anterior descending artery (LADa) flow was measured and the LADa constricted by a micrometer to restrict resting flow by 50%, 75%, and 100%. Adenosine was infused either systemically ($n = 9$), to maintain mean aortic pressure at 50–60 mm Hg, or directly into the LADa ($n = 9$), to create maximal coronary hyperperfusion; no adenosine was infused in the control group ($n = 9$). With systemic adenosine, during each constriction aortic pressure, left ventricular first derivative (LV dP/dt), and heart rate (HR) decreased: aortic pressure by 56.1% ± 2.9% (mean ± SEM), LV dP/dt by 36.2% ± 2.2%, systemic resistance by 42.7% ± 5%, and HR by 38.7% ± 3% during 50% constriction ($P < 0.05$ for each variable). Intracoronary adenosine decreased only aortic pressure, LV dP/dt, and HR, all to a lesser extent: aortic pressure by 5% ± 2.8%, LV dP/dt by 15% ± 1.2%, and HR by 4.6% ± 1.7% ($P < 0.05$, compared with systemic adenosine for each variable). With systemic adenosine only in the nonischemic area, regional myocardial blood flow increased and remained high, from 224.6 ± 65.2 to 342 ± 46.2 $\text{mL}\cdot\text{min}^{-1}\cdot 100\ \text{g}^{-1}$ during 50% constriction ($P < 0.05$); with intracoronary adenosine, ischemic zone regional myocardial blood flow increased, but not consistently. In the ischemic area, O_2 consumption was less with than without systemic adenosine; also, lactate flux production was less positive (−60.2 ± 37.6 compared with 80.3 ± 20.2 $\text{mmol}\cdot\text{min}^{-1}\cdot 100\ \text{g}^{-1} \times 10^{-3}$ during 50% constriction; $P < 0.05$). Systemic infusion of adenosine during coronary hypoperfusion improves regional metabolism during ischemia and, thus, may mitigate myocardial ischemia. The mechanism by which systemic infusion improves metabolic status may be by decreases in both systemic pressure and systemic vascular resistance.

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Primarily an arterial and coronary vasodilator (1) and a sinus node inhibitor (2), adenosine can be used for controlled hypotension (3) and may counter hemodynamic and metabolic impairment (4) during myocardial ischemia. Adenosine may also produce intramyocardial redistribution (5) and "steal" (6). The ratio of O_2 supply to demand, however, plays a major part in adenosine production by the heart (7). When an imbalance occurs, as during hypoxia or ischemia, the myocardium releases adenosine in an amount sufficient to depress myocardial conduction and activity (8), which restores the ba ance of the supply/demand ratio. Endogenous c exogenous adenosine can retard ischemia by one c two mechanisms: by means of special receptors (atr al, ventricular, or even endothelial) (9) or by preven ing metabolic changes in myocardial cells, eithe directly by affecting adenosine triphosphate (AT (10,11) or indirectly by simulating glycolysis an glucose uptake, which increases cellular ATP (12 The specific receptor mechanism may be identified b analyzing the role of systemic hemodynamic variables (for example, pressure, resistance, and heart rat [HR]) in the metabolic response to ischemia. Also, th metabolic effect of adenosine can be evaluated b examining its direct effect on the myocardial metabolic variables, glucose uptake, and consumption c O_2 and lactate.

Adenosine may be a useful agent to induce hypotension in patients with ischemic heart disease Therefore, the rationale for undertaking this stud was to evaluate whether using adenosine to induc

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hypotension during ischemia would be beneficial and, if so, to identify the mechanism of action: local myocardial or systemic-peripheral. We hypothesized that adenosine may minimize regional metabolic impairment during myocardial ischemia. The amount of adenosine, however, was likely to be critical because too much in the coronary circulation could induce steal, and a systemic overdose, simply by decreasing arterial pressure, might decrease both O_2 and blood supply. By a method previously used to study nitroglycerin clinically (13), we compared the hemodynamic and regional metabolic effects of systemic infusion of adenosine with those of intracoronary infusion of adenosine during partial or complete constriction of the left anterior descending artery (LADa) in a canine model of acute coronary artery occlusion (14,15).

Methods

The study was approved by the appropriate institutional review board; animal resource facilities in which this research was conducted are fully accredited by the American Association for Accreditation of Laboratory Animal Care.

Surgical Preparation

Adult male and female mongrel dogs (n = 35), weighing 21–30 kg, received thiamylal (10–15 mg/kg), followed by a continuous infusion of 1–4 $mg \cdot kg^{-1} \cdot h^{-1}$. Each dog was mechanically ventilated with an air/O_2 mixture to maintain normoxia and normocarbia. Catheters were introduced into the pulmonary artery (PA) and aorta (Ao) from the femoral vein and artery, respectively, to measure cardiac output (by thermodilution technique) and pressures. After a left fifth interspace thoracotomy, the heart was suspended in a pericardial cradle. The left ventricle (LV) was cannulated from its apex with a transducer-tipped catheter (Millar) to measure LV pressure and its first derivative (LV dP/dt). The left atrium was cannulated by a rigid catheter for microsphere injection.

The LADa was isolated proximal to the first major apical diagonal branch and loosely encircled by a cardiac pacing wire coated with a polyvinyl chloride ligature (the wire came originally with a T-5, breakaway Keith needle, No. 277934). Resting flow in the LADa was measured by an electromagnetic sinewave flowmeter probe (model BL-613, Biotronex Laboratory, Kensington, Md.) that was 2, 2.5, or 3 mm in diameter according to the vessel diameter. The probe was placed at the isolation site of the LADa, at least 1 cm distal to the ligature (to avoid interference with the fit of the probe around the vessel during constriction). Flow to the LADa was controlled mechanically by a micrometer (NSK #Q01-1 series MV30, SISCO Institutional Industrial Sales, Ocala, Fla.); the micrometer screw gauge, which was sited proximal to the flowmeter probe, was used to manipulate the sling (ligature-wire) encircling the LADa. The exact location of the ligature was selected so that a 10–15-s occlusion of the LADa produced cyanosis of the cardiac apex. Teflon catheters (24 gauge) were placed into the LADa distal to the ligature, into the adjacent coronary vein (LADv), and into a distal circumflex vein (CFXv) (16). The catheters were fixed in place by using a 5-0 prolene suture placed into the epicardium adjacent to the point at which the catheter entered the vessel.

Experimental Protocol

For each animal, flow to the LADa was reduced by 50%, 75%, and 100% from resting level for 15 min each, separated by 1 h of no constriction. Thus, after 15 min of LADa constriction, the ligature was released to allow normal perfusion for 1 h, after which another 15 min of constriction to a greater degree occurred. By arbitrary assignment, adenosine (No. 1177302, Eastman Kodak Co., Rochester, N.Y.) either was infused intravenously from before the first constriction to the end of the experiment to keep Ao pressure at 50–60 mm Hg (n = 10) or was infused before constriction into the LADa distal to the constriction site at a rate titrated to maximal hyperperfusion (maximal LADa flow achieved) with <10% change from baseline of all hemodynamic variables (n = 13), or no adenosine was infused before or during constriction (n = 12, control group). Data were collected before and at the end of each LADa occlusion.

Measurements

Electrocardiogram (standard lead II) and HR were recorded continuously; cardiac output was measured in triplicate with 5 mL of 4°C injectate and a thermodilution cardiac output computer (model 9520A, Edwards Laboratories). The PA, Ao (systolic, diastolic, and mean), LV end-diastolic (post-"A"-wave), and LADa pressures and LV dP/dt (obtained electronically) were recorded continuously by using the Millar catheter (LV) or calibrated Gould-Statham P 50 transducers (LADa, PA, and Ao). Rigid, saline solution-filled polyethylene tubing (Cobe), 4 ft long, connected the PA and Ao transducers and the respective catheters. All standard transducers were calibrated with a mercury manometer and checked for drift before each measurement. The directly visualized LADa was taken as the zero reference for calibration. The flowmeter probes were calibrated before use in saline solution and then zeroed electronically and manually by constricting the vessel.

The cardiac index, stroke volume index (SVI), left ventricular stroke work index (LVSWI), and total systemic and pulmonary vascular resistances were calculated from measured variables by accepted hemodynamic formulas (17).

In all dogs, before and at the end of each LADa constriction period, blood was sampled from the Ao, PA, LADa, LADv, and CFXv for measurement of arterial blood gas tensions, pH, hemoglobin O_2 saturation (IL 282 co-oximeter, Instrumentation Laboratories, Lexington, Mass., calibrated for canine blood), and concentrations of lactate (model 27, Yellow Springs Instruments Co., Ohio), glucose (Accucheck, bG model 790, Bio Dynamics, Indianapolis, Ind.), sodium, and potassium (Lytening 1 instant ISE by AMDEV) and for calculation of base excess or deficit. Regional myocardial blood flow (RMBF) (14) was calculated for both normal and ischemic regions of the myocardium by using accepted formulas (18). For both normal and ischemic myocardium, a single transmural RMBF value was calculated from the corresponding endocardial and epicardial emission data representing approximately 6 g of myocardium.

Statistical Methods

Data from each dog were collated to allow group comparisons. Analysis of variance for repeated measure design (ANOVA PC) with post hoc testing by the Duncan test was used to determine significant variability within groups. The range of the systemic dose of adenosine was 400–600 $\mu g \cdot kg^{-1} \cdot h^{-1}$; the range of the intracoronary dose was 15–20 $\mu g \cdot kg^{-1} \cdot h^{-1}$; and the volume of adenosine infused into the LADa was 0.05–0.1 mL/min.

The control group was used to test the effect of constriction alone on the variables (that is, difference between different levels of constrictions without any adenosine). Data from groups that received adenosine were analyzed to determine the effect of the drug; therefore, data from the control and adenosine groups were compared statistically by the unpaired *t*-test with the Bonferroni correction. Frequency of occurrences was compared between groups by Fisher's exact test. The relationship of ischemic regional flow to LADa flow was determined by least-squares linear regression techniques. Alpha set at a level of <0.05 was considered significant. Results are expressed as mean ± SEM.

Results

One dog in the control group did not survive the entire experiment; two in the control group and two in the intracoronary group had a baseline coronary flow too low to allow accurate control of flow by constriction; and one in the systemic group and tw in the intracoronary group had coronary anomali that did not allow dissection or constriction accordir to the protocol. Thus, data from 8 of the 35 dogs we excluded from the analysis, and the three groups d not differ by number of dogs lost to study or t number actually studied (*n* = 9 for each group Ventricular fibrillation, which was treated by electr cal defibrillation, occurred during LADa occlusion during reperfusion in three dogs in the control grou two of which were successfully defibrillated ($P <$ 0.0 compared with adenosine groups, according to Fis er's exact test). Correlation (*r*) between LADa flo and ischemic zone RMBF in the control group w 0.87 (y-intercept of 1.65 ± 24.8). The baseline hem dynamic and metabolic data were similar for all do before any constrictions, except that HR, LV dP/d and potassium were lower in the intracoronary grou (Tables 1 and 2) (potassium in the LADv was 2.5 0.2 mEq/L compared with 3.2 ± 0.2 mEq/L wi control [$P < 0.05$]). In both adenosine groups befo constriction, flow in the LADa was higher th baseline or control (Table 2).

Effects of Coronary Constriction Alone

During each constriction of the LADa, flow (perce reduction in resting flow) and pressure decrease SVI, LVSWI, and LV dP/dt decreased; and system and pulmonary vascular resistances increased (mai ly during 100% constriction) (Table 1). During eve constriction, in coronary venous blood from the isch mic area pH was decreased, and P_{CO_2}, base deficit, a potassium and lactate concentrations increased (Ta 1). Also, in the LADa region (ischemic zone) duri constriction, delivery and consumption of O_2 and t ratio between them decreased; extraction and co sumption of lactate became significantly negative (in cating net production); and glucose extraction i creased, but not significantly (Table 1).

Systemic Effects of Adenosine

With systemic administration of adenosine befo and during each constriction, HR; Ao, LADa, a systolic LV pressures; LVSWI; LV dP/dt; and system vascular resistance decreased (Table 2). With intr coronary administration of adenosine before any co striction, only systolic LV pressure, LVSWI, and L dP/dt decreased; during constriction, only HR, A pressure, systolic LV pressure, LADa pressur LVSWI, and LV dP/dt decreased, but to a less extent than in the control group (a significant diff ence from systemic adenosine) (Table 2). Before a during constriction with systemic adenosine, SVI w significantly higher than baseline or control SVI.

Table 1. Systemic Hemodynamic and Regional Metabolic Variables in a Canine Model of Myocardial Ischemia

	50% Constriction		75% Constriction		100% Constriction	
	Before constriction	During constriction	Before constriction	During constriction	Before constriction	During constriction
Systemic hemodynamic variables						
LADa flow (mL/min)	39.1 ± 3.7	19.4 ± 1.8[a,b]	32.8 ± 2.4[b]	8.6 ± 0.6[a,b]	28.9 ± 2.5[b]	1.1 ± 0.6[a,b]
LADa pressure (mm Hg)	126.3 ± 7.7	63.3 ± 4.5[a,b]	135.9 ± 8.2	46.9 ± 4.3[a,b]	130.6 ± 8.6	31.6 ± 4.2[a,b]
SVI (mL·beats^{-1}·m^{-2})	27.5 ± 2	24.2 ± 1.8	22.2 ± 2.1	22.2 ± 1.3[b]	21.1 ± 1.7[b]	16 ± 1.5[a,b]
LVSWI (g·m^{-2}·beats^{-1})	42.9 ± 4.2	37.7 ± 3.5	39.2 ± 4.1	33.8 ± 3	32.8 ± 3.3	22.6 ± 3.3[a,b]
LV dP/dt (mm Hg/s)	2271 ± 78	2150 ± 72	2143 ± 117	1933 ± 167[b]	1943 ± 157[b]	1800 ± 169[b]
Vascular resistance (dyne·s^{-1}·cm^{-5})						
Systolic	2894 ± 332	3207 ± 334	3453 ± 289	3506 ± 314	3987 ± 443	4744 ± 552[a,b]
Pulmonary	461 ± 50	524 ± 59	549 ± 54	617 ± 37	632 ± 58	893 ± 131[a,b]
Arterial blood gas values and electrolytes in venous blood from the ischemic area						
pH	7.37 ± 0.2	7.26 ± 0.02[a–c]	7.33 ± 0.01	7.24 ± 0.03[a–c]	7.35 ± 0.03	7.2 ± 0.04[a–c]
P_{CO_2} (mm Hg)	50.2 ± 2.5	59.7 ± 4.3	49.1 ± 2.1	62.4 ± 4.6[a–c]	48.8 ± 2.5	66.2 ± 5.2[a–c]
Base excess	1.7 ± 1.5	−0.6 ± 1.0	0.5 ± 1.2	−2.6 ± 1.4[a,b]	−0.7 ± 1.3	−3.6 ± 1.9[a–c]
Lactate (mmol/L)	1.2 ± 0.2	2.9 ± 0.3[a–c]	1.1 ± 0.2	3.5 ± 0.6[a–c]	1.0 ± 0.1	4.6 ± 0.6[a–c]
Potassium (mEq/L)	3.2 ± 0.2	3.3 ± 0.3	3.0 ± 0.4	3.3 ± 0.3	2.8 ± 0.3	3.5 ± 0.2[a]
Metabolic variables in the ischemic area						
O_2 delivery	10.5 ± 1.3	5 ± 0.6[a,b]	9.3 ± 0.9	2.3 ± 0.2[a,b]	8.1 ± 0.5	0.3 ± 0.1[a,b]
O_2 consumption (mL·min^{-1} × 10^{-2})	7.5 ± 1.0	3.9 ± 0.5[a,b]	6.8 ± 0.7	1.8 ± 0.2[a,b]	5.8 ± 0.6	0.3 ± 0.1[a,b]
Ratio of O_2 delivery to consumption	1.4 ± 0.1	1.3 ± 0	1.4 ± 0.1	1.3 ± 0	1.4 ± 0	1.1 ± 0.1[a,b]
Glucose extraction (%)	15.5 ± 8.3	4.1 ± 5.9	15.6 ± 8.7	21.4 ± 7.4	10.3 ± 8.1	20.1 ± 5.6
Lactate consumption (mmol·min^{-1} × 10^{-3})	14.6 ± 6.5	−22.0 ± 5.2[a,b]	11.7 ± 4.1	−18.1 ± 3.7[a,b]	9.1 ± 3.3	−1.2 ± 0.6[a,b]
Lactate extraction (%)	22.5 ± 11.2	−68.3 ± 13.8	24.8 ± 10.8	−227.2 ± 86.2[a–c]	19.2 ± 5.1	−231.4 ± 48.8[a–c]

LADa, left anterior descending coronary artery; SVI, stroke volume index; LVSWI, left ventricular stroke work index; LV dP/dt, LV pressure and its first derivative.

Values are mean ± SEM.

[a] $P < 0.05$ compared with before that level of constriction in the same group.

[b] $P < 0.05$ compared with baseline (not shown) in the same group.

[c] $P < 0.05$ compared with nonischemic area (not shown) at same level of contriction.

Regional Effects

Reactive hyperemia in the coronary artery was lower with adenosine, systemic or intracoronary, than without it (Table 3). Before and during constriction, resistance (LADa ratio of pressure to flow or to ischemic zone RMBF) decreased with either systemic or intracoronary adenosine (Figure 1). The calculated resistance for zone flow during 100% constriction decreased more with intracoronary adenosine than with systemic adenosine (Figure 1, bottom). With intracoronary adenosine before constriction, LADa pressure was similar to that without adenosine and similar to the baseline value for both adenosine groups, but the decrease was less than with systemic adenosine (Table 2). In both adenosine groups before constriction, flow to the LADa was higher than baseline or control. During constriction, RMBF in the nonischemic area increased with systemic adenosine and was higher than in the control group; RMBF increased in the ischemic area but did not differ significantly from control (Table 4). During constriction, ischemic zone RMBF was higher with intracoronary adenosine than in the control group, but this effect was not consistent (Table 4). During constriction with or without adenosine, the RMBF endocardial/epicardial ratio decreased in the LADa area and did not differ among the groups. During constriction, O_2 delivery, electrolytes, glucose concentration, and potassium and glucose extractions were affected similarly in the nonischemic and ischemic areas during constriction in all groups. During constriction in both adenosine groups, lactate extraction (arteriovenous [a − v] percent difference) was less negative (negative = net production) in the ischemic area compared with control values in the nonischemic area (Figure 2). Only with systemic adenosine was lactate con-

Table 2. Hemodynamic Effects of Systemic and Intracoronary Infusion of Adenosine in a Canine Model of Myocardial Ischemia

		50% Constriction		75% Constriction		100% Constriction	
	Baseline	Before constriction	During constriction	Before constriction	During constriction	Before constriction	During constriction
Measured hemodynamic variables							
HR (beats/min)							
Systemic	154 ± 8	106 ± 9^{a}	94 ± 6^{a,b}	100 ± 7^{a,b}	94 ± 6^{a,b}	97 ± 6^{a,b}	98 ± 8^{a,b}
Intracoronary	120 ± 6^{b,c}	123 ± 4	114 ± 7^{b,c}	102 ± 7^{a,b}	103 ± 7^{a,b}	96 ± 6^{a,b}	94 ± 7^{a,b}
MAP (mm Hg)							
Systemic	136.3 ± 5.7	61.1 ± 1.8^{a}	55.9 ± 1.4^{a,b}	67 ± 3.6^{a,b}	51.5 ± 1.7^{a,b,d}	63.5 ± 4.6^{a,b}	49.8 ± 1.7^{a,b}
Intracoronary	124.1 ± 4	117.6 ± 6.1^{c}	111.3 ± 4.9^{a,c}	105.9 ± 7$^{a–c}$	97.2 ± 6.9$^{a–c}$	99.3 ± 8.5$^{a–c}$	100 ± 9.3$^{a–}$
SLVP (mm Hg)							
Systemic	158.3 ± 6.3	106.7 ± 7.8^{a}	89.4 ± 3.6^{a,b,d}	95 ± 5.7^{a,b}	86.7 ± 5^{a,b}	94.4 ± 7.1^{a,b}	77.2 ± 4.7^{a,b}
Intracoronary	146.1 ± 7.3	133.3 ± 8.7^{a,c}	130 ± 8.3^{a,c}	119.4 ± 10.1^{a,b,d}	116.7 ± 11.8^{a,c,d}	114.4 ± 12.2^{a,b}	105 ± 11.9^{a}
LADa pressure (mm Hg)							
Systemic	108.4 ± 4.8	64.3 ± 6.8^{a}	42 ± 3.0^{a,b,d}	52.3 ± 4.6^{a,b}	27 ± 2.4^{a,b,d}	46.3 ± 5.2^{a,b}	11.4 ± 2.1^{a,b}
Intracoronary	106.4 ± 6	106.3 ± 5.8^{c}	54.7 ± 8.5^{a,d}	89.1 ± 8.9^{b,c}	38.3 ± 7^{a,d}	86.9 ± 9.5^{b,c}	24.6 ± 3^{a,c,d}
LADa flow (mL/min)							
Systemic	36.0 ± 3.2	46.2 ± 7.4^{a}	18 ± 1.5^{a,d}	42.8 ± 6.2	10.6 ± 1.5^{a,d}	48.9 ± 7.4^{a}	0.8 ± 0.5^{a,d}
Intracoronary	30.1 ± 2.3	63.8 ± 6.1^{a,c}	17.4 ± 3.1^{a,d}	53.3 ± 5.8^{a,b}	9.9 ± 2^{a,d}	46.4 ± 5.4^{a,b}	0.3 ± 0.3^{a,d}
Calculated hemodynamic variables							
LVSWI ($g \cdot m^{-2} \cdot beats^{-1}$)							
Systemic	56.2 ± 4.8	32.5 ± 2.4^{a}	26.8 ± 2.2^{a,b}	34.7 ± 2.5^{a}	25.5 ± 3.1^{a,d}	32.4 ± 4.5^{a}	21.7 ± 2.8^{a,d}
Intracoronary	53.8 ± 7.3	45.8 ± 7.2^{a}	41.7 ± 7.3^{a,c,d}	41.3 ± 7.5	35.2 ± 5.7^{a,d}	30.7 ± 5^{a}	27.0 ± 4.4
LV dP/dt (mm Hg/s)							
Systemic	1733 ± 82^{b}	1322 ± 138^{a}	1111 ± 25^{a,b,d}	1178 ± 100^{a,b}	922 ± 119^{a,b}	944 ± 107^{a,b}	900 ± 142^{a,}
Intracoronary	1567 ± 78^{b,c}	1400 ± 53^{a}	1333 ± 71$^{a–c}$	1222 ± 80^{a,b}	1078 ± 94^{a,b,d}	1044 ± 118^{b}	867 ± 124^{b,}
SVI ($mL \cdot beats^{-1} \cdot m^{-2}$)							
Systemic	33.5 ± 2.3	45.5 ± 2.6^{a}	41.5 ± 3.6^{a,b}	45.4 ± 4.6^{a,b}	43.7 ± 4.6^{a,b}	42.6 ± 4.4^{a,b}	37.1 ± 3.8^{b}
Intracoronary	34.5 ± 4.3	30.4 ± 4^{c}	29.9 ± 4.9	30.8 ± 4.8^{c}	28.8 ± 4.4^{c}	24.2 ± 3.1^{c}	22.2 ± 3.6^{a,c}
SVR ($dyne \cdot s^{-1} \cdot cm^{-5}$)							
Systemic	2287 ± 156	1128 ± 93^{a}	1293 ± 133^{a,b}	1339 ± 139^{a,b}	1128 ± 91^{a,b}	1425 ± 188^{a,b}	1277 ± 147^{a,}
Intracoronary	2814 ± 416	3089 ± 560^{c}	3287 ± 599	3518 ± 759^{c}	3437 ± 672^{c}	4037 ± 578^{c}	5285 ± 1204^{a}
PVR ($dyne \cdot s^{-1} \cdot cm^{-5}$)							
Systemic	321 ± 28^{b}	315 ± 28	342 ± 43^{b}	332 ± 25^{b}	368 ± 31^{b}	323 ± 36^{b}	366 ± 33^{b}
Intracoronary	445 ± 64	549 ± 129^{c}	495 ± 96	560 ± 145	592 ± 149	630 ± 135^{c}	959 ± 242^{a,}

HR, heart rate; MAP, mean arterial pressure; SLVP, systolic left ventricular pressure; LADa, left anterior descending artery; LVSWI, left ventricular strol work index; LV dP/dt, first derivative of LV pressure; SVI, stroke volume index; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance.

Values are means ± SEM.

$^{a}P < 0.05$ compared with baseline in the same group.

$^{b}p < 0.05$ compared with no adenosine (not shown) at the same level of constriction.

$^{c}P < 0.05$ compared with systemic adenosine at the same level of constriction.

$^{d}P < 0.05$ compared with before that level of constriction in the same group.

sumption ([a − v] × RMBF) less negative (Figure 2), and O_2 consumption (C[a − v]O_2 × RMBF) decreased more, which resulted in a higher delivery/consumption ratio in the ischemic area (Table 5).

Discussion

Systemic Use of Adenosine

The major finding of this study is that systemically infusing adenosine to induce hypotension during myocardial ischemia decreased O_2 demand by decreasing HR, global contractility, and systemic and pulmonary vascular pressures and resistances. Ader osine also induced redistribution of blood flow an decreased ischemic zone coronary resistance. A these effects together decreased myocardial O_2 cor sumption and lactate production in the ischemi zone. Data from the present study suggest that usin systemic adenosine to induce hypotension wi counter hemodynamic and metabolic impairmer during myocardial ischemia; these results agree wit other studies (4,19–21).

In the dog, barbiturate anesthesia can alter th baroreceptor reflex and thus lead to a high resting H (22). Therefore, decreased HR is very significant i

Table 3. Flow Changes and Reactive Hyperemia Due to Constriction of the Left Anterior Descending Coronary Artery

	Constriction		
	50%	75%	100%
Postconstriction flow (mL/min)			
No adenosine	86.7 ± 7.6[a]	92.6 ± 5.9[a]	82.3 ± 3.5[a]
Intracoronary adenosine	81.2 ± 6.1[b]	69.2 ± 7.2[c]	62.2 ± 10.0
Systemic adenosine	54.4 ± 5.8[c]	65.3 ± 7.2[c]	73.6 ± 7.0[a]
% Change of hyperemia			
No adenosine	131.5 ± 23.5	191.1 ± 21.0	205.2 ± 30.3
Intracoronary adenosine	32.3 ± 11.9[c,d]	42.4 ± 19.4[c,d]	55.6 ± 21.8[c,d]
Systemic adenosine	29.2 ± 11.7[c,d]	63.7 ± 15.2[c,d]	69.9 ± 29.4[c,d]

Values are mean ± SEM.

[a] $P < 0.05$ compared with before that level of constriction (not shown) in the same group.

[b] $P < 0.05$ compared with systemic adenosine at the same level of constriction.

[c] $P < 0.05$ compared with baseline (not shown) in the same group.

[d] $P < 0.05$ compared with no adenosine at the same level of constriction.

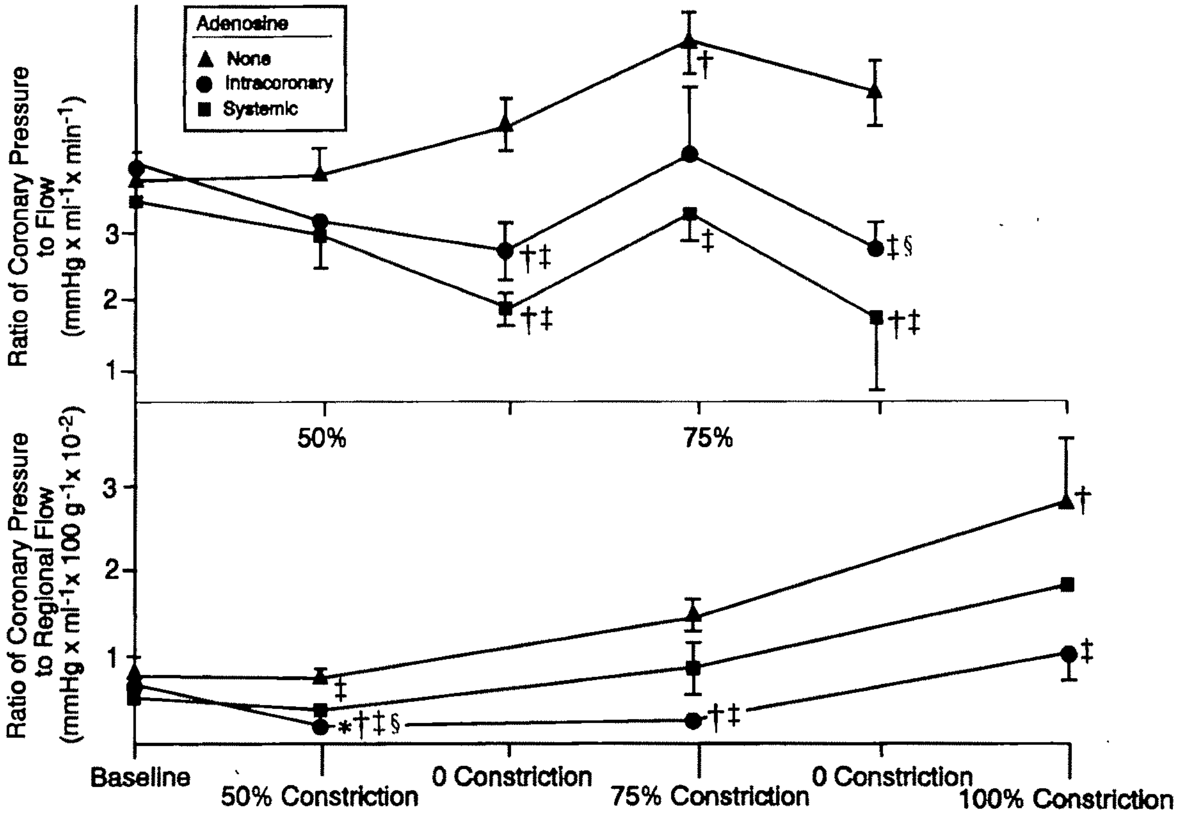

Figure 1. Coronary resistance calculated in two ways (by LADa flow [*top panel*] and RMBF [*bottom panel*]) before and during constriction of the LADa in dogs that did or did not receive adenosine. *$P < 0.05$ compared with before that level of constriction in same group; †$P < 0.05$ compared with baseline in the same group; ‡$P < 0.05$ compared with no adenosine at the same level of constriction; and §$P < 0.05$ compared with systemic adenosine at the same level of constriction.

this setting. In experiments where baseline spontaneous HR is low as that with adenosine infusion in this study, a baroreceptor may mediate a compensatory increase. In this case, O_2 consumption may increase during adenosine infusion, which may adversely affect the O_2 supply/demand ratio; however, in our present experiment, this was not the case. The significant decrease in HR that we observed with either systemic or intracoronary adenosine may have counteracted the underlying barbiturate anesthetic and potential tachycardia. If so, lower HR with a negative chronotropic agent such as adenosine is probably a significant factor in improving myocardial metabolism.

Table 4. Effects of Systemic and Intracoronary Infusions of Adenosine on Regional Myocardial Blood Flow in a Canine Model of Myocardial Ischemia

	Regional myocardial blood flow (mL·min^{-1}·100 g^{-1})					
	Nonischemic area			Ischemic area		
	No adenosine (n = 9)	Intracoronary adenosine (n = 9)	Systemic adenosine (n= 9)	No adenosine (n = 9)	Intracoronary adenosine (n = 9)	Systemic adenosine (n = 9)
Baseline	137.4 ± 27.3	123.3 ± 19.7	224.6 ± 61.1	153.0 ± 34.1	136.5 ± 20.1	189.9 ± 58.8
Flow constriction						
50%	107.8 ± 21.4	313.8 ± 77^{a,b}	341.9 ± 43.2^{c,d}	71.1 ± 11.7^{a,b}	202.3 ± 45.8^{a,b,e}	92.4 ± 17.4^{a,c}
75%	102.1 ± 13.1^{d}	145.2 ± 30.7	284.3 ± 67.2^{d}	24.8 ± 2.7^{b}	95.5 ± 15.5^{c}	61.0 ± 29.1^{b}
100%	89.8 ± 7.6^{a}	73.5 ± 13.4^{d,e}	217.5 ± 39.3^{c,d}	11.4 ± 1.7^{b}	23.9 ± 6.7^{b}	12.1 ± 7.4^{b}

Values are mean ± SEM.
$^{a}P < 0.05$ compared with before that level of constriction (not shown) in the same group.
$^{b}P < 0.05$ compared with baseline in the same group.
$^{c}P < 0.05$ compared with no adenosine at the same level of constriction.
$^{d}P < 0.05$ compared with nonischemic area at the same level of constriction.
$^{e}P < 0.05$ compared with systemic adenosine at the same level of constriction.

The effect of adenosine on arterial pressure also may have influenced the findings. The extent of ischemia, however, may vary inversely with arterial pressure (23); in that case, the depressor effect of adenosine (Table 2) would suppress its beneficial effect. Conversely, the decrease in Ao pressure effected by adenosine in the present study may have improved the regional myocardial O_2 delivery/consumption ratio (Table 5) by decreasing LVSWI (myocardial work), LV dP/dt (contractility), and LV pressure. The net effect of adenosine on myocardial metabolism probably depends primarily on hemodynamic variables. On the other hand, adenosine has the same potential as other metabolites produced during ischemia to have local effects on both the myocardium and the coronary vessels (10–12). Those effects are discussed later in the comparison of systemic with intracoronary effects of adenosine.

The reduction in hyperemia with adenosine reflected the decreased O_2 consumption (Tables 3 and 5). This effect may have resulted from both the initial vasodilation before constriction and from a lower need for O_2 in the myocardium (lower arterial pressure). Hyperemia may also be directly related to arterial pressure, maximal vasodilation making coronary flow completely pressure dependent.

Systemic Effect of Adenosine Compared With Its Intracoronary Effect

Without constriction, systemic adenosine induced hypotension (Ao pressure, systolic LV pressure) with bradycardia (HR), decreased contractility (LV dP/dt), and decreased systemic and coronary resistances. The peripheral effect of adenosine, however, accounted for only part of the metabolic protection because intracoronary administration with minimal peripheral effects (Table 2) still minimized to some extent metabolic impairment during coronary hypoperfusion. Both systemic and intracoronary adenosine, however, played a role in metabolic protection, considering the preserved or improved lactate extraction and O_2 delivery/consumption ratio in the ischemic zone (Table 5, Figure 2). A local metabolic effect can be expected with adenosine because of its direct effect on ATP (10,11) (reducing consumption of ATP) and its indirect effect on glucose metabolism (increasing cellular ATP) (12).

Adenosine did not increase LADa flow during constriction because the constriction was designed to decrease basal LADa flow by the same percent each time. We did find, however, significant changes in LADa flow before constriction and in RMBF measured by microspheres during constriction. Before constriction, coronary resistance was decreased with systemic or intracoronary adenosine (Figure 1, top); the decrease during constriction, however, was more apparent with intracoronary than systemic infusion (Figure 1, bottom).

The subendocardial/subepicardial perfusion ratio decreased to the same extent during constriction with or without adenosine. Therefore, maximal coronary dilation by adenosine did not change the subendocardial/subepicardial perfusion ratio according to some studies, including our data (24–26). On the other hand, submaximal doses of adenosine have preferentially dilated the subendocardium, which may result in a high subendocardial/subepicardial perfusion ratio according to one study (24), but had no effect in another study (27) and the opposite effect in an

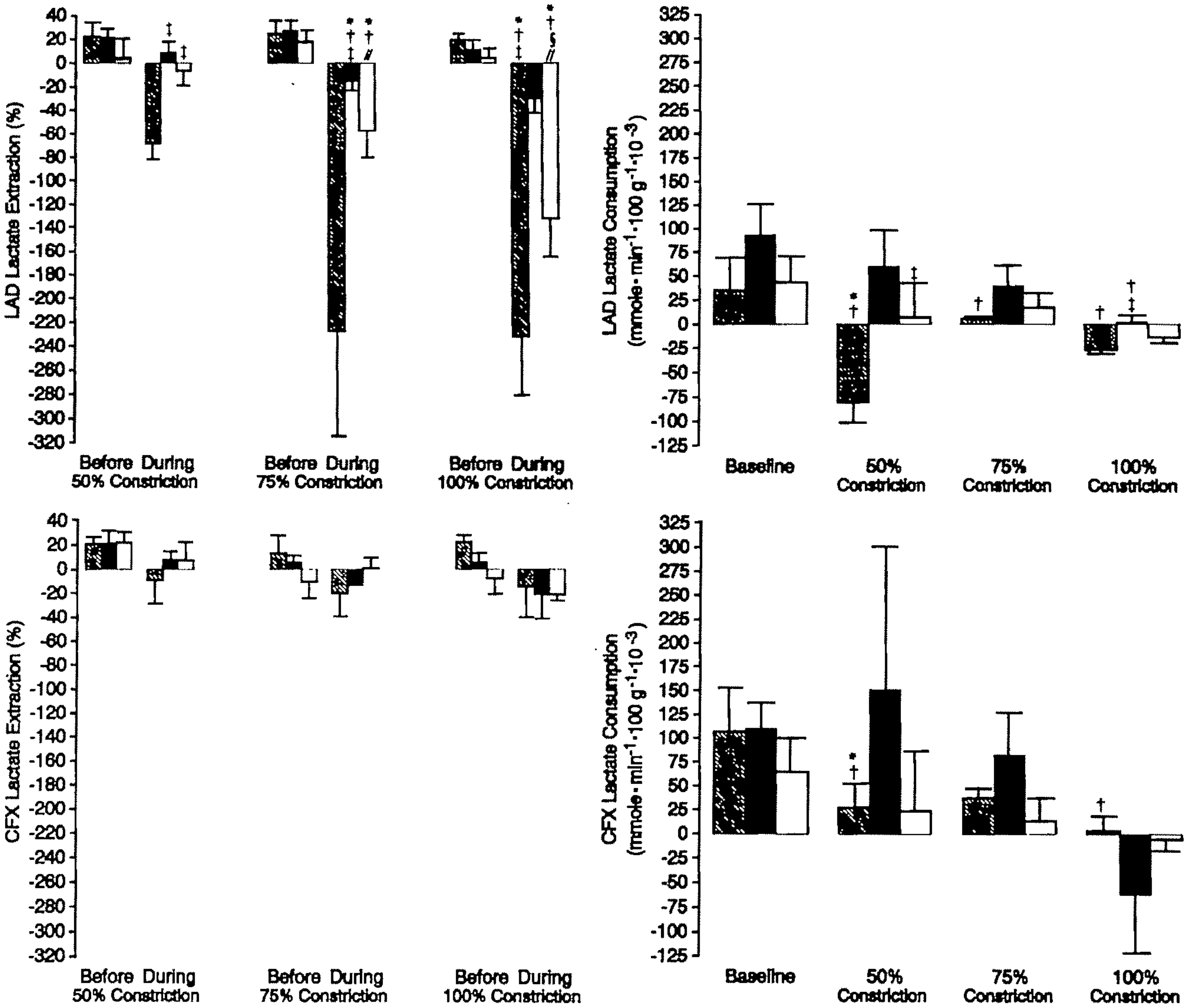

Figure 2. Effect of constriction of LADa on regional lactate metabolism in the ischemic zone (LAD) and nonischemic zone (CFX) in dogs that did or did not receive adenosine. Adenosine was administered to treatment groups at all time periods but baseline. *$P < 0.05$ compared with before that level of constriction in same group; †$P < 0.05$ compared with baseline in the same group; ‡$P < 0.05$ compared with no adenosine at the same level of constriction; §$P < 0.05$ compared with systemic adenosine at the same level of constriction; ||$P < 0.05$ compared with nonischemic area at the same level of constriction. LAD, left anterior descending coronary artery; CFX, circumflex vein; Extraction, arteriovenous % change (a − v/a). Hatched bar, control; solid bar, systemic; open bar, intracoronary.

isolated Langendorff preparation (28). These discrepant data may be related to differences in Ao pressure and HR in the various preparations (29) and in our study (30) to various factors, such as the different experimental design (single stenosis as opposed to multistenotic) and the different amount of adenosine.

We could not demonstrate steal, even though with intracoronary adenosine only distribution of flow was increased in the ischemic region, and in the nonischemic region with systemic adenosine in this model. To document steal, the LADa should be totally constricted, and the circumflex arterial flow must be reduced. Therefore, this is not a good model of steal.

Experimental Ischemic Model

Several aspects of the experimental model used in this study require consideration. The flow probe was used only as a guide to constriction, not to correlate flow values with RMBF. Technical problems, however, with the false-positive effect of constriction are possible. In the control group, LADa flow correlated closely with ischemic zone RMBF ($r = 0.87$; y-intercept 1.65). Thus, apparently the position of the ligature relative to the probe did not affect measurements of flow despite potential collapse of the vessel during constriction. Next, dogs usually have substantial cor-

Table 5. Effects of Systemic and Intracoronary Infusions of Adenosine on Oxygen Metabolism in the Ischemic Area in a Canine Model of Myocardial Ischemia

	No adenosine (n = 9)	Systemic adenosine (n = 9)	Intracoronary adenosine (n = 9)
Oxygen consumption ($\text{mL}\cdot\text{min}^{-1}\cdot 100\ \text{g}^{-1} \times 10^{-2}$)			
Baseline	29.3 ± 6.2	28.9 ± 9.2	19.5 ± 2.3
Flow constriction			
50%	14.2 ± 1.3	8.1 ± 1.4[a–c]	27.4 ± 5.9[d]
75%	4.9 ± 0.7	6.7 ± 2.6[b]	12.1 ± 2.8
100%	2.4 ± 0.4	0.7 ± 0.3[b,c]	3.3 ± 1.2[b]
Ratio of oxygen delivery to oxygen consumption			
Baseline	1.4 ± 0	1.5 ± 0.1	1.6 ± 0.1
Flow constriction			
50%	1.2 ± 0	2.2 ± 0.1[c]	1.7 ± 0.2
75%	1.3 ± 0	1.8 ± 0.2[c]	1.5 ± 0.1
100%	1.4 ± 0	2.5 ± 0.5[b]	1.6 ± 0.1

Values are mean ± SEM.

[a] $P < 0.05$ compared with before that level of constriction (not shown) in the same group.

[b] $P < 0.05$ compared with baseline in the same group.

[c] $P < 0.05$ compared with no adenosine at the same level of constriction.

[d] $P < 0.05$ compared with systemic adenosine at the same level of constriction.

onary collateral circulation and normal collateral vessels; we isolated a single coronary artery only to create ischemia, which differs from the clinical situation in which multiple coronary lesions of various lengths and degrees of stenosis are often present. Deleterious effects observed in this model are likely to be amplified in humans; on the other hand, the beneficial effects related to the substantial collateral blood flow in the dogs might not occur in humans who do not have the chronic coronary constriction that would create collateral channels.

Given the usually substantial flow network in canine myocardium, it may seem unreasonable to consider the LADa and CFXv samples obtained during LADa constriction as representative of totally ischemic and totally normal myocardium, respectively. Even during adenosine infusion, lactate concentration increased slightly, and lactate extraction became negative (significantly less than in the ischemic zone, but this still indicates lactate production or spillout) in the nonischemic (CFXv) region. Because the amount of this production (Figure 2) did not differ significantly from before constriction but did differ significantly from that in the ischemic zone (LADa), this probably indicates some contamination of those venous samples with blood from the ischemic area (14,15). Overall, arterial blood gas and metabolic changes differed markedly between the LADa and the CFXv perfusion areas during LADa constriction (Table 1, Figure 2), which indicates a severely ischemic state in the LADa perfusion area.

Calculation of lactate output and production in the ischemic region was done in two different ways (Figure 2): lacate extraction (percent change [a − v]), which is the conventional means, and lactate consumption ([a − v] × RMBF). The consumption calculation takes into account flow to the area as well as (a − v) lactate difference, whereas lacate extraction does not take blood flow into account. A difference between these two forms of calculation could have been related to the actual change in blood flow to the ischemic area. When flow decreases, evacuation of lactate decreases, and that increases the measured lactate concentration (millimoles per liter) in venous samples from the ischemic area (30). In fact, lactate extraction failed to differ distinctly between systemic and intracoronary adenosine, but lactate consumption did (Figure 2). Similar calculations that took blood flow into the ischemic region into consideration (Table 5) were done for regional O_2 delivery and consumption. Clearly, quantifying the degree of anaerobic metabolism requires calculation of the actual mass of O_2 used and lacate produced, not just the arteriovenous O_2 content difference and lactate (a − v) percent change.

To conclude, our study does indicate that systemic use of adenosine during moderate-to-severe coronary constriction and resultant hypoperfusion could mitigate myocardial ischemia. Clinical trials of adenosine for vasodilation and for inducing hypotension are needed. Intracoronary infusion of adenosine did not provide as much metabolic protection as systemic adenosine. The local effect on myocardial performance and regional myocardial blood flow is beneficial but is only partially responsible for improved metabolic outcome during ischemia. The effect of adenosine on peripheral hemodynamics, which is associated with decreased myocardial afterload, must combine with the local effect of adenosine to achieve a maximal therapeutic effect.

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Effect of Thoracic Epidural Anesthesia Combined With General Anesthesia on Segmental Wall Motion Assessed b Transesophageal Echocardiography

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Patients scheduled for vascular surgery are considered at risk for perioperative cardiac complications. Choice of anesthetic in such patients is guided by a desire not to adversely affect myocardial function. On the basis of data from laboratory studies, thoracic epidural anesthesia (TEA) has been advocated to prevent myocardial ischemia. The aim of this study was to assess whether TEA combined with general anesthesia has any effect on segmental wall motion (SWM) monitored by transesophageal echocardiography in these patients. Patients received alfentanil, midazolam, vecuronium, and 50% N_2O in oxygen, and ventilation was controlled after orotracheal intubation; 12.5 mL of 2% lidocaine HCl was injected through an epidural catheter placed at T6-7 or T7-8. Hemodynamic measurements and transesophageal echocardiographic recordings were obtained before and 10, 20, 30, 40, and 60 min after lidocaine injection. Segmental wall motion was graded a posteriori by two independent experts on a predetermined scale (from 1 = normal to 5 = dyskinesia). A decrease ≥2 grades was considered an SWM abnormality indicative of ischemia. Thoracic epidural anesthesia induced a decrease in systemic arterial blood pressure, heart rate, and cardiac index. The SWM score decreased slightly from 1.34 ± 0.68 to 1.27 ± 0.64 (mean ± SD) (at 10 and 20 min, respectively) ($P < 0.05$). Patients were a posteriori analyzed according to whether they had documented coronary artery disease or not. The SWM score before TEA was significantly higher in patients with documented coronary artery disease (1.51 ± 0.88 vs 1.17 ± 0.51, respectively; $P < 0.05$) and did not change significantly after TEA. A small but statistical decrease in the SWM score was documented in the other patients (1.08 ± 0.27 at 40 min). Ephedrine was injected intravenously in two patients because of systemic hypotension >30%. In these two patients, ephedrine induced reversible SWM abnormalities that may be related to ischemia. Thoracic epidural anesthesia combined with general anesthesia did not worsen or improve SWM in patients at risk for myocardial ischemia; however, correction of hypotension with ephedrine may induce ischemia in these patients.

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Coronary artery disease (CAD) is common in patients undergoing vascular surgery (1). Because cardiac complications are the major cause of perioperative morbidity (2) and myocardial infarction is the most common cause of postoperative mortality in these patients (3), anesthetic technique is an important issue.

Use of a combined technique of epidural anesthesia plus general anesthesia for aortic vascular surgery remains controversial (4,5). A combined technique can increase perioperative intravascular fluid requ ments; may be more likely to result in signific hypotension with release of the aortic cross-clam the patient has an inadequate intravascular fl volume; takes extra time to initiate; and may exp the patient to the additional risk of two anesth techniques, particularily if the epidural block is formed at the thoracic level (5).

In contrast, numerous studies have demonstra a beneficial effect of thoracic epidural anesth (TEA) on the heart and coronary circulation (6– Indices of both myocardial oxygen supply and mand are decreased by TEA, and coronary perfus remains matched to myocardial O_2 consumption spite decreased mean arterial blood pressure (M and coronary perfusion pressure (6–11). Thor epidural anesthesia reverses ST segment chan

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induced by experimental coronary artery occlusion and, in dogs, reduces the anatomic extent of experimentally induced infarcts (6,7). In patients with unstable angina pectoris, TEA can relieve chest pain (8) and increase lumen diameters of stenotic coronary arteries without increasing diameters of nonstenotic arteries (10). These studies may explain the earlier results of Reiz et al. (12) who demonstrated less intraoperative myocardial ischemia (measured by ST segment depression, myocardial lactate extraction, myocardial hypoxanthine production, and cardiac dysrythmias) and lower reinfarction rates in patients with recent myocardial infarction (<3 mo) who underwent predominantly iliac or abdominal aortic surgical procedures under a combined technique of general anesthesia plus low or mid-TEA, respectively, compared with a randomized group receiving general anesthesia alone (12). Thus, there may be beneficial reasons to combine TEA, which blocks the cardiac sympathetic fibers, with general anesthesia in patients with CAD undergoing surgical procedures associated with significant perioperative cardiac morbidity.

Segmental wall motion (SWM) and wall-thickening abnormalities are sensitive and early indices of myocardial ischemia (13,14), and transesophageal echocardiography (TEE) easily detects these changes. Moreover, TEE is better than electrocardiographic (ECG) and capillary pulmonary artery pressure monitoring for early detection of ischemic events (13). On the other hand, the accuracy of TEE is influenced by changes in afterload.

Other than the Reiz et al. (12) study, all of the studies demonstrating beneficial cardiac effects of TEA were performed either in animals or in humans receiving TEA alone and usually limited to T1-5 (6–10,15,16). Obviously, a combined technique has different hemodynamic and cardiac effects. Because the Reiz et al. (12) results have not been confirmed by other investigators, we decided to investigate the effect of TEA plus general anesthesia on SWM in patients scheduled for aortic vascular surgery.

Methods

After approval of the Ethical Committee of Hôpital Henri Mondor, Université Paris XII, we studied 26 consecutive patients scheduled for major vascular surgery (abdominal aortic aneurysmectomy) under TEA associated with general anesthesia. Patients with symptoms of congestive heart failure who had either a cardiothoracic ratio >0.55 on chest radiograph or a radionuclide angiographic ejection fraction <40% and those receiving inotropic drugs during the protocol were excluded from the study. The diagnosis of CAD was documented preoperatively if at least one of the following was present: (a) a history of angina pectoris; (b) documented previous myocardial infarction; (c) dipyridamole thallium scintigraphy demonstrating hypofixation with or without redistribution of the isotope; or (d) coronary angiography showing a critical stenosis >75% in at least one main coronary vessel.

All patients were premedicated with oral flunitrazepam (1.0 mg) and received their usual cardiovascular medication 1 h before the study began. On arrival in the operating room, a 16-gauge catheter was inserted into a peripheral vein for intravenous colloid infusion. A 20-gauge radial artery catheter was inserted under local anesthesia for continuous monitoring of arterial blood pressure and blood sampling for plasma lidocaine and catecholamine measurements. An epidural catheter was inserted into the epidural space through an 18-gauge Tuohy needle at the T6-7 or T7-8 interspace. A pulmonary artery catheter was introduced through the right internal jugular vein. An ECG lead (CM_5) was placed for heart rate monitoring and detection of ischemic events (Hewlett Packard 5000 monitor, Palo Alto, Calif.). Patients were considered to have ischemia when ST segment depression >1 mm for >1 min occurred. Anesthesia was induced with alfentanil (15 μg/kg IV) and midazolam (0.15 mg/kg IV). Tracheal intubation was facilitated by vecuronium (0.1 mg/kg). Anesthesia was maintained with 50% nitrous oxide in oxygen, and a continuous intravenous infusion of midazolam ($0.15\ mg \cdot kg^{-1} \cdot h^{-1}$) throughout the study period and surgery. After induction of anesthesia, a 5-MHz probe (Vingmed) of two-dimensional TEE was inserted to obtain a short-axis view of the left ventricle at the mid-papillary muscle level. This view is characterized by the circular shape of the left ventricle cavity with the posteromedial papillary muscle imaged at the 11-o'clock position and the anterolateral papillary muscle at the 7-o'clock position. The TEE was monitored continuously during the study. Videotape recordings for 5-min periods were made at regular intervals simultaneously with hemodynamic measurements (before and 10, 20, 30, 40, and 60 min after TEA).

The study began 30 min after induction of general anesthesia to ensure a stable hemodynamic baseline. The following measurements were performed: systolic, mean, and diastolic arterial blood pressures; pulmonary artery occluding pressure (PAOP); systolic, diastolic, and mean pulmonary arterial pressures; cardiac output; and systemic arterial and mixed venous blood gases for calculation of arterial and venous oxygen content and difference. Hemodynamic measurements were performed at six predetermined intervals: before and 10, 20, 30, 40, and 60 min after thoracic epidural injection of 12.5 mL of 2.0%

lidocaine HCl. The TEE short-axis views were recorded at the same time over periods of 2 min each for a posterior wall motion evaluation (Panasonic AG6200).

We measured arterial plasma lidocaine concentrations with an immunofluorescence technique (Abbott TDX) at the same time as hemodynamic measurements. The intra- and interassay coefficients of variation for lidocaine dosage were 5%. Simultaneously, arterial blood samples were collected in chilled, heparinized tubes and immediately centrifuged at 4°C for 10 min for plasma catecholamine (epinephrine and norepinephrine) measurements. The plasma was stored at −80°C until assay. Plasma epinephrine and norepinephrine concentrations were calculated twice for each sample using a double-isotope radioenzymatic assay with intra- and interassay coefficients of variation of 8% and 12%, respectively (17).

A colloid infusion (Plasmion) was administered at a rate of 10 mL/kg over a 40-min period beginning 10 min before the epidural injection of lidocaine to maintain a constant PAOP. When MAP decreased >30% below the preanesthetic values, an ephedrine (3–9 mg IV) bolus dose was administered. After the study had been completed, surgery was performed with the same anesthetic technique and monitoring.

The TEE data of each patient were analyzed on two separate occasions by two independent experts unaware of the patient's condition and hemodynamic profile during the study. The left ventricle was divided arbitrarily into four segments for SWM analysis: anterior, posterior, inferior, and septal. The SWM was scored (13) using the following grading system: 1 = normal wall (good thickening and >30% segment shortening); 2 = mild hypokinesia (slightly reduced thickening and 10%–30% segment shortening); 3 = severe hypokinesia (<10% segment shortening and minimal thickening); 4 = akinesia (no thickening and no segment shortening); and 5 = dyskinesia (wall thinning). A decrease ≥2 grades was considered indicative of ischemia. Interobserver discrepancies defined as a SWM evaluation ≥1 grade difference were resolved by a third experienced expert as a consensus.

Hemodynamic, left ventricular SWM, and plasma lidocaine and catecholamine data were analyzed using analysis of variance for repeated measures and a modified paired and unpaired Student's *t*-test; $P < 0.05$ was considered significant. Data are expressed as mean ± SD.

Results

No complications resulted from TEE probe insertion or use or from any other monitoring or anesthetic technique. Two patients were analyzed separately for SWM and hemodynamic variables after they had received intravenous ephedrine for treatment of hypotensive episodes occurring 10 and 40 min after lidocaine injection (MAP 50 mm Hg in each case). The reason for this was that ephedrine induced changes in SWM and in hemodynamics different from those observed under TEA.

Twenty-two men and two women were analyzed together. Mean patient age was 65 ± 8 yr, mean weight was 69 ± 12 kg, and mean height 170 ± 8 cm. Thirteen patients had hypertension, and 15 were receiving chronic cardiac medication (Table 1). Eleven of the 24 patients had CAD documented preoperatively (Table 1).

Norepinephrine, but not epinephrine, plasma levels significantly decreased at all measurement times after lidocaine epidural injection (Table 2). Plasma lidocaine values never reached toxic range (Table 2).

Hemodynamic data are reported in Table 3. A significant decrease in heart rate, MAP, cardiac index (CI), and estimated coronary artery perfusion pressure occurred at all measurement times after TEA. A small but statistically significant increase in PAOP occurred at 20, 40, and 60 min after TEA.

Transesophageal echocardiography revealed 23 SWM abnormalities in 11 patients before epidural lidocaine injection that were located predominantly in the inferior (38%) and septal (29%) wall segments. After epidural anesthesia, SWM abnormalities improved by 1 grade in 9 of these 23 segments and worsened in none. Four new SWM abnormalities (SWM score worsening from 1 to 2) were observed after TEA, two of which returned to baseline by the next study period 10 min later. The mean SWM scores revealed a small but statistically significant decrease after TEA (Table 3).

The subgroup hemodynamic data and SWM scores in patients with (CAD group) and without previously documented CAD (NCAD group) (Table 1) were analyzed and compared a posteriori. Baseline hemodynamics did not differ significantly between the two groups (Table 4). The hemodynamic change induced by TEA differed only slightly between the groups. Heart rate, MAP, and coronary perfusion pressure decreased in both groups, but CI decreased only in the CAD group. The PAOP remained stable in the CAD group but increased significantly (from 7 to 9 mm Hg) at 20, 40, and 60 min after TEA in the NCAD group.

The baseline mean SWM score was significantly less in the NCAD group compared with the CAD group (1.17 ± 0.51 vs 1.51 ± 0.88, respectively; $P < 0.05$). The mean SWM score did not change after TEA in patients with CAD but showed a small but statistically significant decrease in the NCAD group. Before TEA, there were 10 SWM abnormalities in four patients in the NCAD group and 13 SWM abnormal-

Table 1. Coronary Artery Disease and Cardiac Medical Therapy in 24 Patients Undergoing Vascular Surgery

Pt No./gender	Angina pectoris	MI	Ischemia ECG (leads)	Dipyridamole thallium redistribution	Coronary angiography	Previous CABG	HTN	Drug therapy
1/M	–	—	—	—	—	–	–	—
2/M	–	—	—	Negative	—	–	+	α,N
3/M[a]	–	Inferior	V_5V_6	—	—	+	–	—
4/M	–	—	—	Negative	—	–	+	N
5/M	–	—	—	—	—	–	+	CaB,αβ
6/M	–	—	—	—	—	–	+	ACE
7/M	–	—	—	—	—	–	+	αβ
8/M[a]	–	Septal	V_1V_2	—	—	–	–	β
9/M	–	—	—	—	—	–	+	CaB
10/M	–	—	—	—	—	–	–	—
11/F	–	—	—	—	—	–	+	—
12/M[a]	–	—	V_5V_6	—	—	–	+	ACE,α
13/M	–	—	—	—	—	–	+	ACE,CaB
14/M[a]	–	Inferior	II,III,VF	—	—	–	+	αβ
15/F	–	—	—	—	—	–	+	—
16/M	–	—	—	—	—	–	–	—
17/M	–	—	—	—	—	–	–	—
18/M[a]	–	Inferior	II,III,VF	—	—	–	–	β,N
19/M[a]	+	—	—	—	3 stenosis	–	–	N,CaB
20/M[a]	–	—	—	Anterior	—	–	–	—
21/M[a]	–	—	—	Anterobasal	—	–	–	—
22/M[a]	+	Inferior	II,III,VF	—	—	–	–	CaB,N
23/M[a]	–	—	II,III,VF	—	—	–	+	CaB
24/M[a]	–	Inferior	III	—	—	–	+	αβ,CaB,N

α, α-Adrenergic blockers; αβ, α- and β-adrenergic blockers; ACE, angiotensin converting enzyme inhibitors; β, β-adrenergic blockers; CaB, calcium blockers; CABG, coronary artery bypass graft surgery; CAD, coronary artery disease; ECG, electrocardiogram; HTN, hypertension; MI, myocardial infarction; N, nitrate; Pt, patient.

[a] Evidence of CAD.

Table 2. Lidocaine and Catecholamine Plasma Concentrations

Time (min)	Lidocaine (μg/mL)	Epinephrine (pg/mL)	Norepinephrine (pg/mL)
0	1.08 ± 0.49	646 ± 130	49 ± 26
10	3.35 ± 1.02[a]	487 ± 111[a]	38 ± 19
20	2.97 ± 0.86[a]	439 ± 123[a]	45 ± 23
30	2.67 ± 0.70[a]	395 ± 96[a]	36 ± 18
40	2.43 ± 0.56[a]	407 ± 104[a]	37 ± 20
60	2.04 ± 0.48[a]	435 ± 111[a]	41 ± 23

Mean ± SD.

[a] $P < 0.05$, comparison with t = 0 (analysis of variance for repeated measures).

ities in seven patients in the CAD group. These SWM abnormalities improved in three and six patients, respectively; two new SWM abnormalities occurred in each group.

There was no interobserver variability ≥2 grades with regard to SWM analysis. The overall interobserver correlation for SWM grading was 96%. A third observer resolved disagreements of 1 grade difference in SWM score in 12 cases. The SWM could not be analyzed in 12 of the 552 total segments available for analysis.

Two patients who documented an important decrease (>30%) in systemic MAP received ephedrine. The SWM was analyzed but the results were considered separately. In both cases, although SWM was judged normal before and after epidural anesthesia when the hypotension occurred, intravenous ephedrine injection was followed by abnormalities in the inferior and septal segments, graded 4 and 5, respectively. One of these patients demonstrated ST segment depression (ECG lead CM_5) after ephedrine injection when systemic MAP increased from 50 to 65 mm Hg and heart rate from 40 to 90 beats/min. In the other patient, ephedrine increased MAP from 50 to 60 mm Hg and heart rate from 90 to 106 beats/min. Abnormalities in SWM resolved within a few minutes without treatment when heart rate returned to values documented before ephedrine injection. These two patients had an uneventful perioperative course, with no change in postoperative ECG or increase in creatine kinase-MB documented postoperatively.

Discussion

In agreement with previous studies (11,12), we observed that the combination of TEA plus general

Table 3. Hemodynamic Variables and Segmental Wall Motion

	Time (t) (min)					
	0	10	20	30	40	60
HR (beats/min)	61	56^a	54^a	54^a	54^a	54^a
SD	10	10	9	9	9	9
MAP (mm Hg)	83	69^a	66^a	66^a	66^a	69^a
SD	23	16	17	15	15	16
PAOP (mm Hg)	7.9	8.1	9.0^a	8.3	8.8^a	8.8^a
SD	3.4	3.2	3.5	3.2	2.9	3.5
CI ($L \cdot min^{-1} \cdot m^{-2}$)	2.4	2.3^a	2.2^a	2.2^a	2.2^a	2.2^a
SD	0.6	0.5	0.5	0.5	0.5	0.4
CPP (mm Hg)	53	45^a	42^a	42^a	41^a	43^a
SD	17	12	11	11	10	9
SWM	1.34	1.27^a	1.27^a	1.28^a	1.27^a	1.28^a
SD	0.68	0.64	0.64	0.66	0.65	0.64

HR, heart rate; MAP, mean arterial blood pressure; PAOP, pulmonary artery occlusion pressure; SWM, segmental wall motion; CI, cardiac index; CPP, estimated coronary perfusion pressure (diastolic blood pressure − PAOP).

^{a}$P < 0.05$, comparison with $t = 0$ (analysis of variance for repeated measures).

Table 4. Segmental Wall Motion Abnormalities Score and Hemodynamic Variables in Patients With No Documented and Documented Coronary Artery Disease

Time	SWMA		HR (beats/min)		MAP (mm Hg)		PAOP (mm Hg)		CI ($L \cdot min^{-1} \cdot m^{-2}$)		CPP (mm Hg)	
(min)	NCAD	CAD	NCAD	CAD	NCAD	CAD	NCAD	CAD	NCAD	CAD	NCAD	CAD
0	1.17^a	1.51	64	58	83	83	7.2	8.7	2.2	2.6	60	47
±SD	0.38	0.88	12	7	25	21	3.2	4.0	0.5	0.7	19	12
10	1.13^a	1.46	57	54	68	72	7.5	8.8	2.2	2.4	48	43
±SD	0.34	0.85	12	8	12	20	2.9	4.3	0.5	0.6	12	11
20	1.11^a	1.46	55	53	65	68	8.7	9.3	2.1	2.3	43	40
±SD	0.32	0.85	11	8	12	22	2.9	4.3	0.4	0.6	10	12
30	1.09^a	1.51	55	53	65	67	8.1	8.5	2.2	2.3	44	40
±SD	0.29	0.88	10	8	12	20	2.5	4.0	0.4	0.5	10	11
40	1.08^a	1.48	54	53	64	69	8.7	9.0	2.2	2.3	42	40
±SD	0.27	0.85	10	7	13	19	2.7	3.3	0.4	0.6	9	11
60	1.09^a	1.51	55	53	67	72	9.0	8.6	2.2	2.3	44	42
±SD	0.29	0.85	10	7	14	17	3.1	4.2	0.5	0.4	7	12

SWMA, segmental wall motion abnormalities; CAD, coronary artery disease; NCAD, no coronary artery disease; HR, heart rate; MAP, mean arterial blood pressure; PAOP, pulmonary artery occlusion pressure; CI, cardiac index; CPP; estimated coronary perfusion pressure.

All data are expressed as mean value ± SD.

^{a}$P < 0.05$ (CAD vs NCAD).

anesthesia decreased MAP, heart rate, CI, and estimated coronary perfusion pressure, but PAOP remained nearly constant owing to colloid infusion. The decrease in CI might be explained by a decreased inotropic effect of TEA related to thoracic sympathetic blockade (6,11,15). Despite the large decrease in estimated coronary perfusion pressure, TEA plus general anesthesia did not worsen SWM or induce myocardial ischemia, even in patients with documented CAD, suggesting that oxygen supply remained equal to oxygen consumption. Coronary artery blood flow is usually maintained during systemic arterial hypotension due to coronary artery vasodilation but can be limited by coronary stenosis where maximal vasodilation occurs only in downstream vessels. Coronary vessel adaptation should have been enhanced by TEA, which has been documented to vasodilate stenosed epicardial coronary arteries (10). Because TEA decreases left ventricular stroke work and increases the diastolic time of coronary perfusion due to the decreased heart rate, this should improve the myocardial oxygen supply/demand ratio. In addition, the decrease in myocardial contractility might have decreased the intramyocardial tissue pressure and the corresponding vascular resistances (18).

In a previous study (19), we demonstrated that lumbar epidural anesthesia induced SWM changes indicative of myocardial ischemia. Discrepancies between our two studies might be explained by the previously described beneficial effects of cardiac sympathetic blockade (7–10) that occur with TEA but not with lumbar epidural blockade. In one case (lumbar epidural blockade), the decrease in systemic arterial pressure and consequently the decrease in coronary artery perfusion pressure may lead to a decrease in coronary artery blood flow, which compromises the myocardial oxygen supply. In the other case (TEA), the decrease in cardiac work and in myocardial oxygen demand may compensate for the decrease in coronary artery blood flow. Any increase in cardiac work may nevertheless lead to myocardial ischemia, as illustrated by the two patients who received ephedrine.

Ephedrine, which has both α- and β-adrenergic properties, increases both heart rate and arterial blood pressure, thus increasing oxygen consumption and reducing oxygen supply by a decrease in diastolic time (20). The changes in SWM observed in the two patients treated with ephedrine suggest that significant hypotension during TEA was well tolerated and perhaps preferable to pharmacologic manipulations aimed at increasing coronary perfusion pressure when no TEE or ECG evidence of myocardial ischemia is present.

Detection of ischemia with TEE does have some limitations. We monitored the wall motion activity at the short-axis view of the left ventricle at the midpapillary muscle level. Although perfusion beds of the three main coronary arteries are usually imaged at this level (21), basal and apical wall motion abnormalities could be missed. Although two-dimensional TEE is a reliable technique for detecting SWM abnormalities (13), it is difficult to quantify wall thickening and endocardial wall motion. To determine wall thickening requires powerful software and measures not possible in real time. Our estimates of wall thickening were therefore qualitative. Measuring endocardial wall motion requires a reference axis. During systole, the center of mass of the left ventricle changes by translation and rotation. Use of either a floating or fixed axis permits analysis but can result in under- or overestimation of the extent of abnormal wall motion (14); however, there is no consensus on the optimal centroid for evaluation of wall motion (14,22). We limited this problem by using the papillary muscles as reference points. Overestimation may occur because of "tethering" (i.e., segments of the myocardium adjacent to ischemic or infarcted segments may display contraction abnormalities related to proximity to the affected segments) (21,23–26). Nevertheless, this effect concerns only 5% of the myocardial circumference (27).

Changes in left ventricular loading conditions result in changes in SWM scores. A decrease in preload or afterload could make normal segments appear hyperkinetic such that abnormal segments would be overgraded. Conversely, ischemic walls might appear to decrease their function when preload or afterload is increased. In this study, preload (estimated by PAOP) remained constant, but afterload decreased, which might have artifactually improved SWM scores.

Hypokinesia may be less specific than dyskinesia or akinesia in detecting myocardial ischemia (28). Although we chose hypokinesia in this study as a threshold for ischemia to increase the sensitivity of the technique, there were no SWM changes indicative of myocardial ischemia. Finally, this study compares SWM after TEA to a control state that follows anesthetic induction. The actual preanesthetic SWM scores by TEE are not available. General anesthesia alone might have induced the SWM abnormalities not reversed by the subsequent epidural anesthesia. Preoperative TEE could address this question, but insertion of the esophageal probe in awake patients is stressful and may induce SWM changes.

We conclude that patients undergoing major vascular surgical procedures are prone to develop myocardial ischemia (29–32). Our study adds further support to the body of information demonstrating a beneficial effect of TEA in patients with CAD; we showed that TEA does not change SWM in these patients despite a significant decrease in estimated coronary perfusion pressure. Correction of hypotension induced by TEA must be monitored carefully because myocardial ischemia related to the increased oxygen demand may occur.

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Role of Systemic Arterial Pressure, Heart Rate, and Derived Variables in Prediction of Severity of Myocardial Ischemia During Acute Coronary Occlusion in Anesthetized Dogs

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The present study examined the postulate that the quotient of mean systemic arterial pressure and heart rate predicts the severity of myocardial ischemia during occlusion of the left anterior descending coronary artery. Studies were performed in open-chest fentanyl-anesthetized dogs before and during halothane ($n = 8$) or isoflurane ($n = 8$) anesthesia. The pressure-rate quotient (PRQ) decreased significantly in both groups during incremental increases in halothane or isoflurane to 68% and 57% of control values at 0.5 MAC and to 41% and 38% at 1.5 MAC for halothane and isoflurane, respectively. Myocardial lactate production was unchanged from the ischemic region, and no correlation between the PRQ and myocardial lactate production was observed. In contrast, heart rate correlated significantly ($r = 0.376$; $P < 0.05$) with lactate production. The product of systolic systemic arterial pressure and heart rate (rate-pressure product) correlated with blood flow ($r = 0.493$; $P < 0.001$) and with oxygen consumption ($r = 0.571$; $P < 0.001$) in the normal myocardium. A weak correlation ($r = 0.330$; $P < 0.05$) of rate-pressure product with myocardial lactate production from the ischemic region was observed. There were no correlations between the PRQ and myocardial lactate production from the ischemic region or indices of blood flow distribution (i.e., inner/outer ratio in the ischemic region or ischemic/normal ratio). The relationship of hemodynamic variables to measurements of regional myocardial metabolism was independent of background anesthetic agent or depth of anesthesia. The current data suggest that heart rate changes are weakly predictive of severity of myocardial ischemia. No interdependence between heart rate and blood pressure on blood flow regulation to ischemic myocardium is evident. The findings indicate that the PRQ has limited prognostic value in the assessment of severity of myocardial ischemia under laboratory conditions.

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Although there is a growing awareness that myocardial ischemia often occurs in the absence of hemodynamic change (1,2), control of heart rate and systemic arterial pressure endures as the sine qua non of safe anesthesia in patients with coronary artery disease (3). Recent laboratory reports (4,5) reinforce this principle and attempt to quantitate the relative contribution of heart rate and blood pressure to changes in myocardial oxygen balance. These studies suggest that the quotient of mean arterial pressure and heart rate (PRQ) provides an "effective" prediction of severity of myocardial ischemia (4,5). In a canine model dependent on nutrient flow through ischemic collateral vessels (4), both collateral/normal and inner/outer flow ratios in the ischemic region correlated significantly ($r = 0.61$ and 0.78, respectively) with the PRQ. Significant but less precise correlations with the elements of the PRQ (i.e., heart rate [HR] and mean arterial pressure) were also described (4). Similar findings were reported in an animal model wherein ischemia was induced by critical stenosis of a coronary artery (5) and worsening ischemia was denoted by systolic wall thickening of the ischemic region. In view of these findings, the authors (4,5) suggest the potential usefulness of the PRQ as a prognostic indicator of myocardial ischemia in humans.

This laboratory previously found no evidence for worsening of myocardial ischemia with halothane or isoflurane during acute coronary occlusion (6). The aim of the present study, in contrast to other reports (4,5), was to characterize HR and systemic arterial

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pressure relationships with respect to regional oxygen supply and demand during more severe ischemia evoked through acute coronary artery occlusion. Direct measurements of regional oxygen supply and demand and regional metabolism were obtained in a canine model in which HR and systemic arterial pressure were free to vary. A secondary aim was to determine the effectiveness of the PRQ as a predictor of myocardial ischemia in the presence of either halothane or isoflurane anesthesia.

Methods

The study was approved by the Institutional Committee for Animal Use and Care of the University of California, Davis, and conducted in accordance with its guidelines.

Animal Preparation

Sixteen mixed-breed male and female dogs weighing 22.9 ± 0.7 kg (mean ± SEM) were used in the experiments. Anesthesia was induced with thiamylal (15 mg/kg), the trachea intubated, and ventilation established with a positive-pressure Harvard respirator. Anesthesia was maintained with nitrous oxide in oxygen and by fentanyl (100 μg/kg IV), followed by a continuous infusion of fentanyl (1–2 $\mu g \cdot kg^{-1} \cdot min^{-1}$); ventilation and fraction of inspired oxygen were adjusted to maintain normoxia and normocapnia. Sodium bicarbonate was given before the study period if base deficit exceeded 5 mEq/L; this was not repeated during the protocol. A semirigid catheter was inserted into the thoracic aorta by means of a femoral arteriotomy for reference blood sampling and aortic pressure measurements. Cardiac output was measured via a pulmonary artery flow-directed catheter by the thermodilution technique using iced saline solution and an Edwards computer (model 9520A, Santa Ana, Calif.); values were averaged from intermittent triplicate measurements.

A left thoracotomy at the fifth intercostal space was performed using aseptic surgical techniques; the pericardium was opened, and a flexible polyethylene catheter was inserted into the left atrium for pressure measurement and injection of radioactive microspheres. Left ventricular (LV) pressure was measured by a Konigsberg micromanometer (model P7, Pasadena, Calif.) inserted through a stab wound in the apex of the ventricle and secured with a pursestring suture. The Konigsberg transducer was calibrated in vitro with a mercury manometer and in vivo with aortic systolic and left atrial pressures. Frequent calibrations were made to eliminate the electrical drift of the transducer. Arterial blood pressure was measured with Statham pressure transducers (model 23dB, Hato Rey, Puerto Rico). A pulsed Doppler flow transducer was placed around the left anterior descending coronary artery (LAD) near its origin, and a ligature snare for future use was placed around the same artery just proximal to its first marginal branch; the flow transducer was used to determine zero flow. After heparinization, two small epicardial veins on the left ventricle in the region of the LAD draining the region distal to the snare and a region outside the distribution of the LAD were cannulated for blood sampling; free drainage of each catheter was allowed.

Arterial and coronary venous samples were collected anaerobically for the measurement of oxygen saturation (IL Co-oximeter 282, Lexington, Mass.) and blood lactate concentrations (YSI 2300 Stat, Yellow Springs Instruments, Yellow Springs, Ohio); incomplete data were obtained in four dogs owing to venous catheter occlusion. Calculation of regional myocardial extraction ratios, production, and consumption for oxygen and lactate were made from arteriovenous concentration differences and regional myocardial blood flow measurements with a modified Fick equation. Body temperature was maintained at >37°C with a heating pad. Hemodynamic data were recorded on a direct writing polygraph (model 2800S, Gould, Cleveland, Ohio) and on an analogue FM tape recorder (Kyowa Electronic Instruments, Tokyo, Japan) for subsequent analysis.

Physiologic Measurements

Variables, including systemic arterial pressures, HR, and cardiac output were measured, and stroke volume, systemic vascular resistance, and pulmonary vascular resistance were calculated with standard formulas. Coronary perfusion pressure was calculated from the difference between diastolic aortic pressure and the LV end-diastolic pressure. The rate-pressure product (RPP) was calculated from the systolic systemic arterial pressure multiplied by the HR and the pressure-rate quotient (PRQ) by the division of mean systemic arterial pressure by HR (4).

Regional blood flow was measured with radioactive microspheres, as previously described (7). In brief, approximately 2–3 × 10^6 microspheres (15 μm) labeled with ^{95}Nb, ^{46}Sc, ^{141}Ce, or ^{85}Sr were injected into the left atrium over 20 s. A reference blood sample was withdrawn from an arterial catheter starting 15 s before the microsphere injection and continuing for 2 min at a constant rate of 7.75 mL/min. The order of the isotopes was randomized. After the experiment was completed, the animal was killed with an intravenous injection of saturated KCl. The sampled organs were then removed, sectioned,

Table 1. Changes in Hemoglobin Concentration, Arterial Blood Gases and Acid-Base Status, and Temperature During Experimental Acute Coronary Occlusion in 16 Dogs

	Before occlusion		After occlusion					
	0 MAC		0 MAC		0.5 MAC		1.5 MAC	
	HAL	ISO	HAL	ISO	HAL	ISO	HAL	ISO
Hg (g/dL)	13.0 ± 0.3	12.5 ± 0.22	12.8 ± 0.5	12.5 ± 0.3	11.7 ± 0.6	11.2 ± 0.3	10.9 ± 0.4	11.0 ± 0.2
Pa_{O_2} (mm Hg)	118 ± 12	119 ± 19	114 ± 12	111 ± 18	134 ± 23	107 ± 16	106 ± 11	102 ± 16
Pa_{CO_2} (mm Hg)	39 ± 1.5	41 ± 0.9	38 ± 2.3	43 ± 1.1	38 ± 2.0	45 ± 1.6	37 ± 2.7	44 ± 1.7
pHa	7.33 ± 0.02	7.35 ± 0.01	7.33 ± 0.02	7.30 ± 0.01	7.33 ± 0.03	7.27 ± 0.02	7.33 ± 0.03	7.30 ± 0.01
BE (mEq/L)	−4.3 ± 0.6	−2.8 ± 0.6	−5.1 ± 0.6	−4.3 ± 0.6	−5.2 ± 0.8	−4.8 ± 0.6	−5.4 ± 0.7	−4.2 ± 0.6
T (°C)	38.4 ± 0.3	37.7 ± 0.2	38.5 ± 0.3	37.9 ± 0.2	38.3 ± 0.2	37.9 ± 0.2	38.3 ± 0.2	37.9 ± 0.2

MAC, minimum alveolar concentration; HAL, halothane; ISO, isoflurane; Hg, hemoglobin; Pa_{O_2}, arterial oxygen tension; Pa_{CO_2}, arterial carbon dioxide tension; pHa, arterial pH; BE, base excess; T, central blood temperature.

Results are presented as mean ± SEM.

weighed, and counted for radioactivity. The LV ischemic region was identified by an intracoronary injection of 0.3 mL of methylene blue at the site of occlusion and a sample was taken with margins >1 cm. Regional blood flow was calculated from the ratio of radioactive count of measured sample and that of reference blood sample.

Experimental Protocol

A period of 1 h was allowed to elapse after instrumentation; nitrous oxide was replaced by nitrogen and ventilation and oxygenation were set to provide normocapnia and normoxia. End-tidal gases were measured throughout the experiment with a Medspect mass spectrometer (AIMT, St. Louis, Mo.).

After baseline measurements were obtained, LAD occlusion was achieved by closure of the ligature snare. Postocclusion hemodynamic variables, myocardial blood flow, and metabolic indices (i.e., oxygen and lactate balance) were measured after 30 min. Dogs were randomized to receive either halothane or isoflurane, and anesthetic concentrations within each agent were administered in randomized order. Steady-state comparisons were made at equianesthetic dosages at low (halothane 0.4%, isoflurane 0.6%) and high (halothane 1.2%, isoflurane 1.8%) alveolar concentrations. Measurements were repeated at each stage of the experiment under stable end-tidal anesthetic gas concentrations.

Data Analysis

Data were compared within and between anesthetic groups at each experimental stage using repeated measures analysis of variance and analysis of covariance, with a significance level set at 0.05. In addition, correlation coefficients were compared for each data set (no volatile agent, halothane, or isoflurane). When no significant differences were detected among data sets, the results were combined to yield a single correlation coefficient value to examine the association between hemodynamic variables and invasive measurements of regional myocardial oxygen supply/demand balance.

Results

Changes in core temperature, hemoglobin values, arterial blood gases, and acid-base status during the course of the experiment are shown in Table 1. The preparation showed good stability, apart from a small decrease in hemoglobin concentrations with time.

There were no significant changes in baseline hemodynamic variables after acute LAD occlusion (Table 2). After LAD occlusion, total myocardial blood flow (MBF) in normally perfused myocardium was 95 ± 5 $mL \cdot min^{-1} \cdot 100\ g^{-1}$ tissue, whereas MBF in the ischemic region was 38 ± 6 $mL \cdot min^{-1} \cdot 100\ g^{-1}$ tissue ($P < 0.001$, compared with the normal region). The inner/outer blood flow ratio in the ischemic region was 0.69 ± 0.08 compared with baseline values of 0.96 ± 0.06 ($P < 0.001$) in the normal myocardium. There were no significant changes in HR, systolic arterial pressure (SAP), diastolic arterial pressure (DAP), mean arterial pressure (MAP), RPP, or PRQ after LAD occlusion (Table 3). Myocardial oxygen extraction from the ischemic region increased significantly in all dogs (Table 3) after LAD occlusion. No evidence of LV failure was apparent according to cardiac output and LV end-diastolic pressure measurements.

With the introduction of a volatile agent, the RPP was not significantly changed at 0.5 MAC values for both agents but decreased at 1.5 MAC to 70% ($P < 0.05$) and 72% ($P < 0.05$) of control values for halothane and isoflurane, respectively

Table 2. Hemodynamic Variables Before and After Acute Left Anterior Descending Coronary Artery Occlusion in 16 Fentanyl-Anesthetized Dogs

Variable	Before occlusion	After occlusion
Heart rate (beats/min)	73.3 ± 6.5	84.4 ± 6.4
Cardiac output (L/min)	2.54 ± 0.15	2.58 ± 0.15
Mean systemic arterial pressure (mm Hg)	95.3 ± 3.7	92.1 ± 5.0
Mean pulmonary arterial pressure (mm Hg)	13.6 ± 0.9	14.4 ± 0.8
Left ventricular end-diastolic pressure (mm Hg)	6.78 ± 0.97	6.88 ± 0.81
Coronary perfusion pressure (mm Hg)	65.1 ± 3.6	65.0 ± 3.9
Systemic vascular resistance (dynes·s·cm^{-5})	2957 ± 198	2868 ± 265
Pulmonary vascular resistance (dynes·s·cm^{-5})	250 ± 28	240 ± 29

Results are presented as mean ± SEM.

(Figure 1). Concomitant decreases in myocardial oxygen consumption ($M\dot{V}O_2$) from normal myocardium at 1.5 MAC to 64% ($P < 0.05$) and 64% ($P < 0.05$) of control values were observed for halothane and isoflurane, respectively (Figure 1). There were significant correlations ($r = 0.571$; $P < 0.001$) between RPP and $M\dot{V}O_2$ (Figure 2) and between RPP and MBF ($r = 0.493$; $P < 0.001$) for the grouped data (Table 4).

The PRQ decreased significantly with the introduction of volatile anesthetics, decreasing to 68% ($P < 0.05$) and 41% ($P < 0.05$) at 0.5 and 1.5 MAC halothane, respectively, and to 57% ($P < 0.05$) and 38% ($P < 0.05$) at 0.5 and 1.5 MAC isoflurane, respectively (Figure 3). There was no significant correlation between PRQ and the ratio of ischemic/normal flow for either agent (Figure 3). Myocardial lactate production from ischemic myocardium was unchanged (Figure 4).

Individual hemodynamic variables were subjected to multiple correlation analysis to determine their relationship with indices of myocardial oxygen supply and demand. There were no significant differences in correlation coefficients among baseline, halothane, or isoflurane groups for the comparisons, and data for each group were combined to yield a single correlation coefficient for each comparison between hemodynamic variable and measures of MBF and metabolism (Table 4).

In the normally perfused region of the left ventricle, SAP ($r = 0.398$; $P < 0.05$), DAP ($r = 0.355$; $P < 0.05$), MAP ($r = 0.394$; $P < 0.05$), and RPP ($r = 0.493$; $P < 0.001$), but not PRQ ($r = 0.198$; P = NS), revealed significant correlations (Table 4) with regional transmural MBF. Significant correlations of SAP ($r = 0.518$; $P < 0.001$), DAP ($r = 0.531$; $P < 0.001$), MAP ($r = 0.551$; $P < 0.001$), RPP ($r = 0.571$; $P < 0.001$), and PRQ ($r = 0.338$; $P < 0.05$), but not HR ($r = 0.061$; P = NS), were observed with $M\dot{V}O_2$ from the normal region.

In ischemic myocardium, correlation coefficients were weak but reached significance for SAP ($r = 0.362$; $P < 0.05$) and MAP ($r = 0.316$; $P < 0.05$), but not DAP, HR, RPP, or PRQ, when correlation analysis with regional transmural MBF was performed (Table 4). There was also a weak association between $M\dot{V}O_2$ from the ischemic region and SAP ($r = 0.389$; $P < 0.05$), DAP ($r = 0.321$; $P < 0.05$), and MAP ($r = 0.367$; $P < 0.05$). The ratio of inner/outer flow in the ischemic region was not associated with any HR or blood pressure variable (Table 4). Myocardial lactate production from the ischemic region showed significant positive correlations for HR ($r = 0.376$; $P < 0.05$) and RPP ($r = 0.330$; $P < 0.05$). The PRQ did not correlate with any measured index of severity of myocardial ischemia.

Independent measures of myocardial regional oxygen supply and demand (MBF, $M\dot{V}O_2$, and myocardial lactate production) in the ischemic region showed no association with the volatile agent used (namely, halothane or isoflurane) or with end-tidal concentrations of the agent.

Discussion

The present data reinforce the concept that the complex interactions that regulate blood flow to normal and ischemic myocardium defy simple description by noninvasive variables such as HR and systemic arterial pressure (8,9). For example, although rate and arterial blood pressure show weak correlations with oxygen supply and demand in normal myocardium, their predictive value in relation to quantification of ischemic flow is poor when they are free to vary. This is not surprising, because the PRQ and RPP encompass only two of the many inputs regulating regional MBF (8–10).

Blood Flow Distribution and Metabolic Effects During Acute Ischemia

It has been successfully argued that HR effects are paramount in either determining the degree of myocardial ischemia or precipitating ischemia during anesthesia (11,12). An increase in HR induces a concomitant increase in blood flow to normal myocardium to match increased metabolic demand, the latter mechanism mediated through the release of local vasodilator factors such as adenosine (13,14). By contrast, it is assumed that in the ischemic bed,

Table 3. Changes in Hemodynamic Variables After Left Anterior Descending Coronary Artery Occlusion in Each Group of Dogs Subjected to Analysis

Variable	Before occlusion, 0 MAC		After occlusion, 0 MAC	
	HAL (n = 8)	ISO (n = 8)	HAL (n = 8)	ISO (n = 8)
HR (beats/min)	70 ± 4.6	73 ± 8.2	83 ± 5.4	81 ± 8.6
SAP (mm Hg)	143 ± 6.4	136 ± 8.9	137 ± 5.9	133 ± 7.8
DAP (mm Hg)	72 ± 5.0	68 ± 4.6	73 ± 3.1	69 ± 4.6
MAP (mm Hg)	95 ± 4.4	91 ± 5.3	94 ± 3.4	90 ± 5.0
RPP (beats·mm Hg·min^{-1})	9948 ± 747	9608 ± 899	11315 ±841	10734 ± 1228
PRQ (mm Hg·min·beats^{-1})	1.42 ± 0.16	1.35 ± 0.16	1.19 ± 0.13	1.17 ± 0.09
O_2 ext				
Normal region	0.59 ± 0.04	0.64 ± 0.04	0.62 ± 0.03	0.66 ± 0.03
Ischemic region	0.60 ± 0.04	0.57 ± 0.03	0.72 ± 0.03*	0.75 ± 0.02*

MAC, minimum alveolar concentration; HAL, halothane; ISO, isoflurane; HR, heart rate; SAP, systolic arterial pressure; DAP, diastolic arterial pressure; MAP, mean arterial pressure; RPP, rate-pressure product; PRQ, pressure-rate quotient; O_2 ext, oxygen extraction.
Results are presented as mean ± SEM.
*$P < 0.05$ compared with control values.

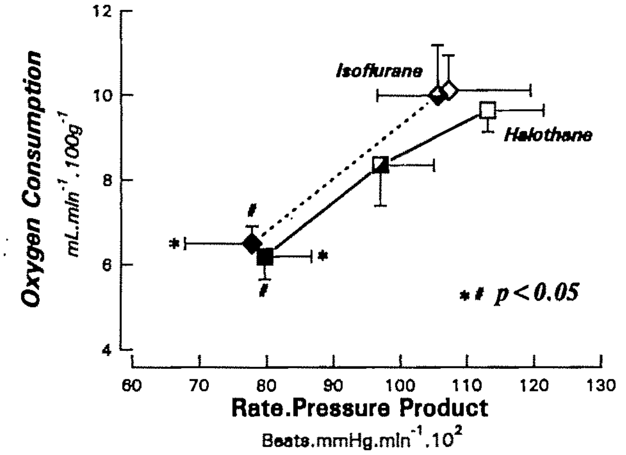

Figure 1. Relationship between the rate-pressure product and myocardial oxygen consumption in normally perfused myocardium under isoflurane (n = 8) or halothane (n = 8) anesthesia. Values represent mean ± SEM. *Open symbols*, mean value under control conditions (0 MAC); *half-solid symbols*, mean values at 0.5 MAC; *solid symbols*, mean values at 1.5 MAC. *Mean value for rate-pressure product is significantly ($P < 0.05$) different from the corresponding control value (open symbol). #Mean value for myocardial oxygen consumption is significantly ($P < 0.05$) different from the corresponding control value (open symbol).

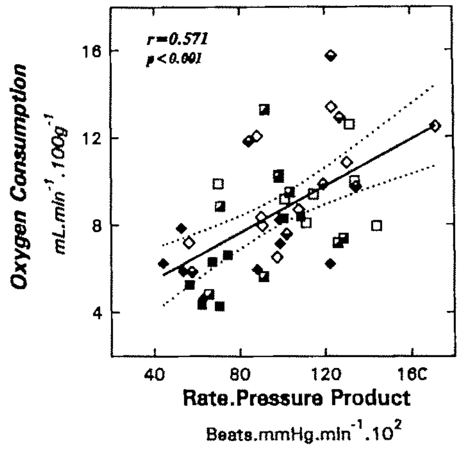

Figure 2. Scatter plot of relationship between rate-pressure product and myocardial oxygen consumption in normally perfused myocardium in 16 dogs. *Solid line*, regression coefficient; *dotted lines*, 95% confidence intervals; other symbols as in Figure 1.

vasodilator reserve is largely exhausted, and therefore the increased metabolic work associated with HR increases cannot be matched by significant increases in flow, thus exacerbating the existing supply-demand imbalance (11,12,15–18). In the present analysis, higher HRs were associated, albeit not strongly, with increased lactate production from the ischemic region.

Several authors (5,16,19,20) have stated that in view of the reliance of ischemic myocardium on collateral flow for oxygen supply, coronary perfusion pressure to the collateral bed becomes critically important to the maintenance of adequate blood flow. In the present study, there were weak associations between systemic pressures and regional MBF and oxygen consumption in the ischemic bed. Yet, in the range of values observed in the present analysis and in our concurrent study (6), there was no adverse redistribution of blood flow from the ischemic region despite a wide range of coronary perfusion pressures (6) submitted to analysis. These data support the postulate that in the canine model, even with acute coronary occlusion, modest vasodilator reserve persists in ischemic myocardium, possibly reflecting the extensive collateralization in the dog. This mechanism (21) can, for the most part, assist in the maintenance of perfusion to the ischemic area, provided that perfusion pressure to the collateral bed remains in the autoregulatory range (22). For example, it is suggested that myocardium may adapt to ischemia by downregulating its energy requirement

Table 4. Correlation Coefficients Describing Associations Among Hemodynamic Variables and Indices of Myocardial Oxygen Supply and Demand

	HR (beats/min)	SAP (mm Hg)	DAP (mm Hg)	MAP (mm Hg)	RPP (beats·mm Hg·min^{-1})	PRQ (mm Hg·min·beats^{-1})
Normal region						
MBF (n = 48)	0.122	0.398[a]	0.355[a]	0.394[a]	0.493[b]	0.198
M$\dot{V}$o$_2$ (n = 47)	0.061	0.518[b]	0.531[b]	0.551[b]	0.571[b]	0.338[a]
Ischemic region						
MBF (n = 48)	−0.158	0.362[a]	0.249	0.316[a]	0.238	0.240
I/O (n =48)	0.054	0.135	−0.041	0.042	0.194	−0.034
M$\dot{V}$o$_2$ (n = 43)	−0.156	0.389[a]	0.321[a]	0.367[a]	0.271	0.277
M$\dot{V}$.Lac (n = 38)	0.376[a]	−0.011	0.085	0.040	0.330[a]	−0.225
Ratios (ischemic/normal)						
MBF (n = 48)	−0.223	0.201	0.093	0.149	0.031	0.155
M$\dot{V}$o$_2$ (n = 43)	−0.220	0.128	0.048	0.088	−0.039	0.114

MBF, myocardial blood flow; M$\dot{V}$o$_2$, myocardial oxygen consumption; I/O, inner/outer flow ratio; M$\dot{V}$.Lac, myocardial lactate production; other abbreviations as in Table 2.

[a] $P < 0.05$.

[b] $P < 0.001$.

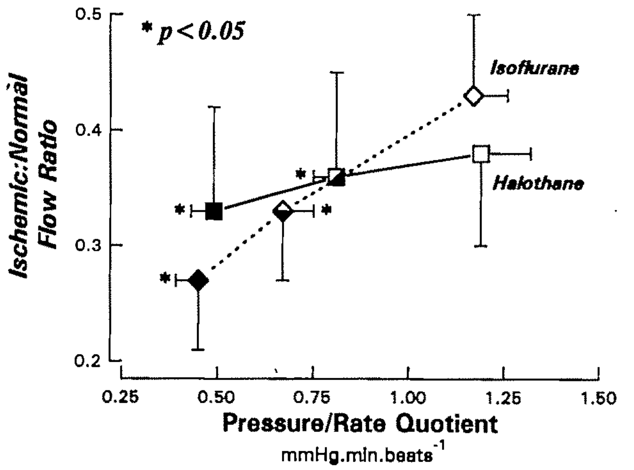

Figure 3. Relationship between pressure-rate quotient and ratio of myocardial blood flow between ischemic region and normally perfused myocardium during isoflurane (n = 8) or halothane (n = 8) anesthesia. Symbols as in Figure 1.

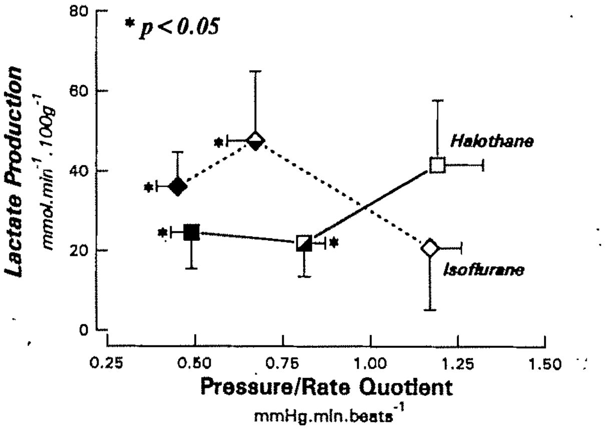

Figure 4. Relationship between pressure-rate quotient and lactate production from an ischemic area of the left ventricle supplied by an occluded coronary artery during isoflurane (n = 8) or halothane (n = 8) anesthesia. Symbols as in Figure 1.

below blood flow-limited rates of energy production (23,24).

Systemic hypertension is also thought to have an adverse impact on myocardial oxygen balance (16,20,25) through increases in myocardial work, which if not matched by increased blood flow to the heart, can lead to worsening ischemia. In the present analysis, this was not found to be a major factor, pointing once again to the previous hypothesis. Of note, in relation to the previous discussion, it has been shown that local vasodilator component mechanisms are restrained during ischemia through neural vasoconstrictor activation (10,26,27). Paradoxically, this response counters the tendency toward transmural steal in the ischemic region (10). Whether disturbances of neurally mediated vasoconstriction play a role in modifying blood flow distribution to ischemic myocardium during halothane or isoflurane anesthesia is a question that remains open to future study.

Limitations of the Present Analysis

Factors regulating blood flow to ischemic myocardium are primarily dependent on factors controlling blood flow to adjacent normal myocardium through collateral beds (8,28) and on local biochemical and mechanical changes affecting vascular tone in the ischemic region (8,28). In the present study, ischemia was evoked through occlusion of the LAD. Therefore, collateral flow hinges on anatomic connections with adjacent myocardium, which in the dog, in contrast to humans, tend to be plentiful but nonetheless do not provide as reliable a safety margin as collateral vessels formed through slow, progressive ischemia. In addition, native collateral vessels are believed to have less vascular reactivity than collateral vessels formed through chronic ischemia (29,30) and may therefore be less likely to respond to a vasodilator stimulus (8). For example, any diminished responsiveness of abruptly opened collateral channels could contribute to our failure to observe any deleterious blood flow redistribution phenomena. Nevertheless, this argument is opposed by studies in similar models (31,32) demonstrating that redistribution of blood away from an ischemic region can be elicited when a powerful local vasodilator stimulus is applied.

In the ischemic region, transmural and inner/outer flow measurements showed considerable variability to LAD occlusion. This was unlikely to be due to an error of tissue sampling, because care was taken to leave wide margins around the sample taken from the ischemic zone. The variability is more likely to be due to between-dog variability in anatomy with respect to collateral flow dependence and problems inherent in using an animal model with native collateral vessels rather than those formed by ischemia. The average flows obtained from the ischemic region are consistent with values obtained by other researchers using similar animal models (31–36).

As mentioned, although there is considerable variability among dogs in response to coronary occlusion, blood flow persists through collateral vessels to the ischemic region, independent of complex changes in hemodynamic variables. This implies that despite conditions that are traditionally thought to induce redistribution of blood flow away from ischemic myocardium through vasodilation of adjacent normal myocardium, there appears to be adequate vasodilator reserve (9) to maintain flow to match myocardial oxygen consumption in the ischemic region. Presumably, provided that coronary perfusion pressure to the collateral bed is maintained above a critical value, even under acute hypoperfusion evoked by coronary occlusion, collateral flow can be further augmented in response to changes in myocardial oxygen demand (i.e., because of inherent collateral vessels, occlusive ischemia is a graded phenomenon and not an absolute ablation of blood flow).

Nevertheless, one consideration that has to be raised in the current investigation is the possibility that infarction may have occurred in some dogs in response to occlusion, and therefore the findings might not be relevant to acute ischemia. Although this possibility cannot be excluded, continuing maximal oxygen extraction and persistent and stable oxygen consumption by the ischemic region indicate that at least some degree of contractile function and functional integrity remained intact, presumably supported by collateral flow. Under these circumstances, the fundamental principles governing collateral flow (8) to the functioning ischemic myocardium should continue to apply.

Comparison With Other Studies

Our findings differ considerably from other studies (4,5) that found a reasonably good correlation between PRQ and collateral/normal and ischemic inner/outer flow ratios during regional hypoperfusion. However, there were a number of major differences between the studies that could account for the disparities. In particular, Buffington et al. (4) induced ischemia over a period of days with an Ameroid constrictor mounted on a coronary artery to induce collateral vessel formation. Therefore, resting collateral flow was greater than that observed in the present study. In relation to the comparison of PRQ with myocardial flow variables, a further divergence resided in their study protocol in which HR was controlled by atrial pacing at rates >96 beats/min (4). In contrast, in the present experiments HR was free to vary and, despite a wide range of values, more than half were <90 beats/min (i.e., the analysis contained more values in the physiologic range normally observed under anesthesia). In animals with higher HRs, higher myocardial oxygen consumption will be observed, possibly leading to greater susceptibility to small reductions in regional myocardial perfusion; whereas in the present analysis, lower HRs may confer a greater margin of safety before adverse changes in ischemic metabolism, such as an increased lactate production, are evident. In the clinical environment, for the quotient to hold any predictive value in determination of myocardial ischemia, it should hold true throughout the normal physiologic range observed in humans under general anesthesia (37,38).

Implications of the Present Analysis

In view of the restrictions applied by Buffington et al. (4), and on the evidence of the present study, the PRQ fails to adequately predict the severity of myocardial ischemia under laboratory conditions when HR, arterial pressure, and myocardial contractility are free to vary. The present data add weight to recent reports (39,40) concerning patients undergoing coronary artery bypass surgery that showed a poor association between hemodynamic correlates and the incidence of myocardial ischemia evidenced by regional wall motion abnormalities.

Although the PRQ has been shown to have little predictive value in the present setting, this does not diminish the importance of control of HR and arterial blood pressure in patients with coronary artery disease (41). The present findings uphold to a limited extent the traditional view that HR increases can be associated with worsening ischemia (1–3). The data also point to the complex interactions that summate to determine regional MBF (8) and the potential of other mechanisms, possibly local or neural (10), to influence myocardial oxygen supply. Heart rate control (3,42), coincident with maintenance of an adequate coronary perfusion pressure (3), remains important to the conservation of blood flow during severe hypoperfusion; however, more research is needed to gain an understanding of mechanisms of ischemia unrelated to hemodynamic events (39).

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PEDIATRIC ANESTHESIA
Section Editor
Paul R. Hickey

Should All Children With Suspected or Confirmed Malignant Hyperthermia Susceptibility Be Admitted After Surgery? A 10-Year Review

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Children otherwise suitable for same-day discharge may be admitted to the hospital solely because they are known or suspected to be malignant hyperthermia-susceptible (MHS). To determine whether their hospitalization is necessary, the medical charts of 303 children labeled MHS who had undergone surgery with anesthesia free of malignant hyperthermia-triggering agents on 431 occasions between 1981 and 1990 were reviewed. Eighteen of these patients (25 cases) who were subsequently identified as biopsy-negative were excluded from the study. We recorded the reason for the MHS label and the perioperative management and outcome of the cases. Fifty-eight percent of procedures were followed by hospital admission solely because of the patient's MHS label. None of the 25 children (33 cases) with biopsy-proven malignant hyperthermia developed intraoperative or postoperative pyrexia. Ten children suspected to be MHS developed pyrexia >38.5°C. These episodes were not considered to be malignant hyperthermia and were not treated with dantrolene. None of the remaining 275 patients exhibited any features of malignant hyperthermia, although one had an adverse reaction to radiologic contrast medium. On the basis of our retrospective analysis, postoperative admission to the hospital solely on the basis of the MHS label is not warranted.

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The label malignant hyperthermia-susceptible (MHS) is conferred after positive muscle biopsy (1). Although many more children are suspected to be MHS because of a family history of malignant hyperthermia (MH) or a previous suspected MH reaction, the incidence of true MHS within this group of children is unknown.

Management of all MHS patients at our hospital, The Hospital for Sick Children, Toronto, Ontario (HSC), has consisted of administering an anesthetic free of MH-triggering agents, followed by monitoring for 4 h in the recovery room and overnight on the ward. The patients are observed for increases in temperature and other features of MH. The surgery itself, however, may not always warrant overnight admission to the hospital. Disadvantages of overnight stay include disruption to the patient and his or her family, increased risk of infection, and increased health care cost (2).

An informal telephone survey of the anesthesia departments of six major North American children's hospitals revealed that all six allow certain suspected MHS children to go home after minor surgery. Although anesthesia without complications has been reported in adults (3–5) and children (6) undergoing muscle biopsy for MH, there is less information available for the effects of anesthesia for other types of surgery in suspected or proven MHS patients (7) and none specifically for children. In particular, the policy of same-day discharge for these children has not been assessed. We therefore retrospectively reviewed the history, management, and outcome of all suspected or proven MHS patients who presented for surgery within a 10-yr period to ascertain the incidence of intraoperative and postoperative complications.

Methods

Malignant hyperthermia-susceptible patients were identified from the following sources at HSC: Health Records' diagnosis database, Patient Operative Care Unit's surgical and Dentistry's booking lists, and Department of Anaesthesia's consultation and muscle biopsy records. From the 303 charts of MHS-proven or MHS-suspected patients who underwent

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431 surgical procedures at HSC over a 10-yr period between January 1, 1981, and December 3, 1990, the following information was recorded for each patient: age, gender, date and nature of the surgery, use of prophylactic dantrolene, and duration of anesthesia.

The reasons for the MHS label were also recorded: positive muscle biopsy, previous suspected MH reaction, previous masseter muscle rigidity (MMR), and first-, second-, or more distant, degree relative with a history of suspected MH reaction or positive muscle biopsy. Eighteen (25 procedures) of the 303 patients recorded as suspected MHS were excluded because of subsequent negative muscle biopsies. During our 10-yr study period, patients with a history of MMR were given the MHS label and were therefore included in our analysis. If MMR was associated with acidosis or other signs of MH, we considered it an MH reaction.

The dates and test centers of muscle biopsies and details of suspected MMR and MH reactions in the children and their relatives were recorded when available. Most biopsies performed in our patients and their relatives were analyzed at Toronto General Hospital (TGH) where, since 1987, 3% halothane has been used in the caffeine halothane contracture (CHC) test, in accordance with the North American Malignant Hyperthermia protocol (8). Before this, a less specific test with 1% halothane was used (9). Variations in test procedures may result in center-to-center differences in specificities (9).

Also noted were axillary temperatures >38.5°C that occurred intraoperatively or postoperatively (within 3 days of surgery) and complications (defined as other adverse events possibly related to MH, such as cyanosis, arterial desaturation, hypercapnia, tachypnea, tachycardia, or muscle rigidity identified as such in the nursing or medical records, irrespective of other causes or whether treatment was required.

Results

Of the 285 patients (406 procedures) included in the study, 168 were male and 117 female. They ranged in age from 2 mo to 19 yr.

Figure 1 illustrates the number of surgical procedures performed and the proportion of patients eligible for same-day discharge. The surgical procedures performed included 39% ear, nose, and throat surgery; 19% dental surgery; 11% orthopedic surgery; 9% general surgery; and 7% urologic procedures. Same-day discharge would have been feasible in 231 (57%) of the 406 cases if not for the MHS label (Figure 1).

All patients received anesthetics free of MH-triggering agents. Duration of anesthesia ranged from 15 min to 6.7 h.

Prophylactic dantrolene (0.5–1.5 mg/kg) was administered to all suspected MHS patients treated before 1985 (10). In addition, 10 children received dantrolene intravenously from 1987 to 1988 during a pharmacokinetics research study (11).

Table 1 summarizes the reasons recorded for the MHS label. Of these 285 patients, 25 (33 procedures) had biopsy-proven MH. Ten patients (15 procedures) had biopsy specimens analyzed at TGH before 1987, and 13 (16 procedures) had their biopsy specimens analyzed at TGH after 1987. Two patients had biopsies performed at other centers.

Information about the acquisition of the suspected MHS label for the remaining 260 patients was frequently incomplete. This was due in part to the retrospective nature of the study: documentation was often poor, and parents or patients lacked information about biopsies or reactions occurring in relatives or at other hospitals. A history of a previous MH reaction was the reason for the suspected MHS label in 23 patients undergoing 36 procedures. Sixteen of these patients had their suspected MH reactions at other institutions. These reactions were most commonly associated with an unexplained rise in temperature and sometimes elevated creatine kinase (CK) levels, acidosis, or admission to an intensive care unit. Of the seven patients who had their previous suspected MH reactions at our hospital, two had MMR accompanied by acidosis, and five had an unexplained rise in temperature accompanied by acidosis.

Masseter muscle rigidity was the reason for the suspected MHS label in 11 patients (13 procedures): 3 patients at other institutions and 8 at our institution. The CK levels were measured postoperatively in five of our patients and did not increase to >6000 U/L in any patient.

Two hundred twenty-six patients (324 procedures) acquired the MHS label because of a relative's positive biopsy or history of a previous MH reaction. Frequently, details were lacking because of incomplete documentation by the anesthetist or the patient's or parents' inadequate knowledge about the details. The most common reason for a child to be suspected MHS was to have a first-degree relative with biopsy-proven MH (63 relatives). The majority of these biopsies (41 relatives) were performed at TGH before 1987. Details about previous MH reactions in first-degree relatives were often inadequate; however, an unexplained rise in temperature was the most frequent presenting sign. Chart information about more distant relatives was frequently vague. Parents may have been aware of a relative's MH reaction or a positive muscle biopsy but knew no other details, or they were not documented.

There were no cases of intraoperative pyrexia

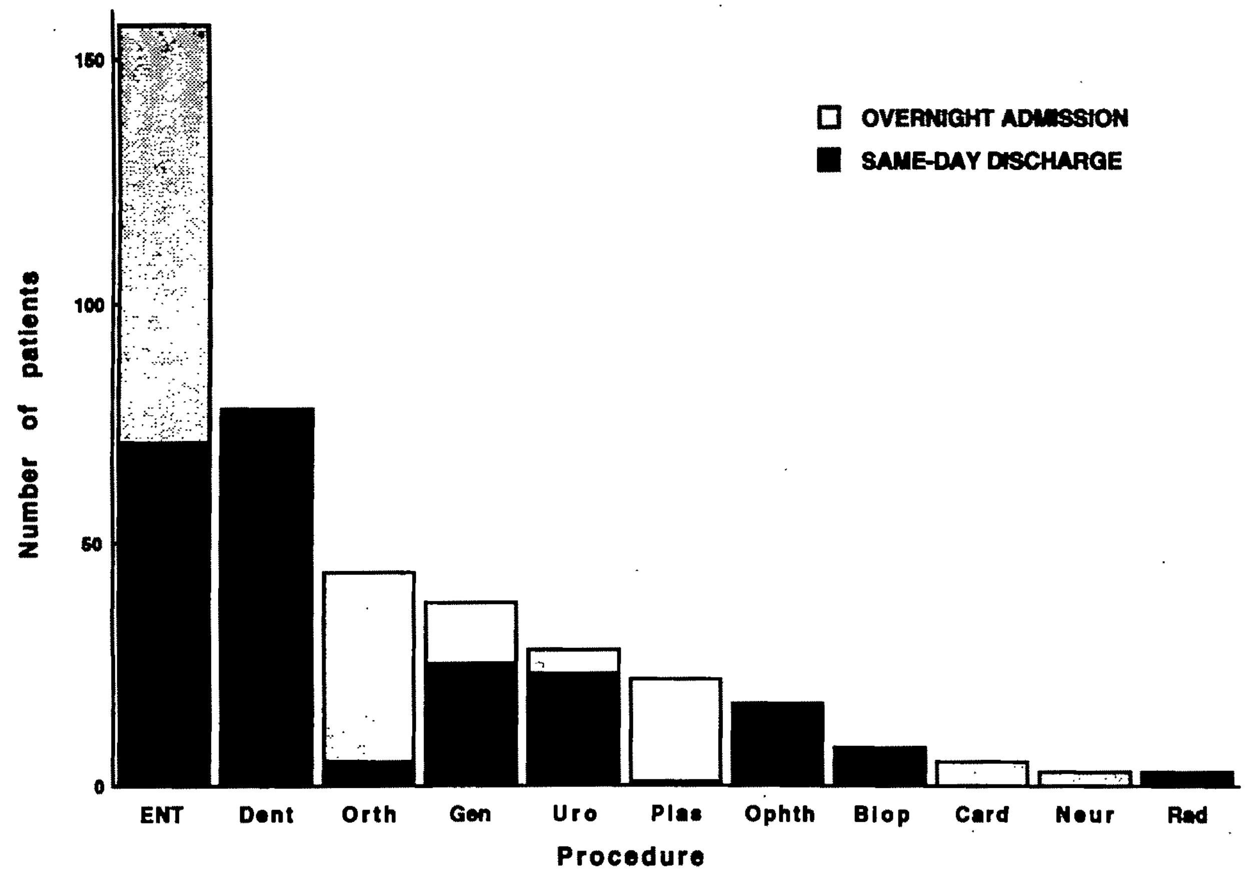

Figure 1. Procedures performed in malignant hyperthermia-susceptible patients. ENT, ear, nose, and throat; Dent, dental; Orth, orthopedic; Gen, general; Uro, urologic; Plas, plastic; Ophth, ophthalmologic; Biop, muscle biopsy; Card, cardiothoracic; Neur, neurologic; Rad, radiologic.

Table 1. Malignant Hyperthermia Susceptibility in Pediatric Patients Undergoing Surgery

Reason for MHS label	Patients (n = 285)	Procedures (n = 406)
Biopsy-positive	25	33
Previous MH reaction	23	36
Previous masseter spasm	11	13
First-degree relative, biopsy-positive	63	100
First-degree relative, previous MH reaction	23	27
Second-degree relative, biopsy-positive	57	79
Second-degree relative, previous MH reaction	24	28
More distant relative, MH reaction or biopsy-positive	59	90

MHS, malignant hyperthermia-susceptible; MH, malignant hyperthermia.

(>38.5°C) in 285 suspected or known MHS patients in our study. None of the 25 biopsy-proven MH patients developed postoperative pyrexia or other signs of an MH reaction. Six of these 25 children had received routine preoperative dantrolene.

Ten (3.5%) of the 285 suspected MHS patients developed postoperative pyrexia (Table 2). Four of these patients had received routine prophylactic dantrolene. An anesthetist examined all 10: in five the fever was due to a cause other than MH; in the remaining five a cause was not determined, but the fever was not thought to be part of an MH reaction and settled after administration of acetaminophen, without sequelae. Of the 10 patients who developed postoperative fever, three had surgical procedures not requiring postoperative admission. Although the fever responded to acetaminophen in all three subjects, these children may have required readmission had they been sent home.

Intraoperative dantrolene was given to a 7-yr-old patient when the pulse rate increased from 160 to 200 beats/min, arterial oxygen saturation decreased from 92% to 89%, and temperature increased to 38.4°C after an injection of radiologic contrast medium during cardiac catheterization. There was no muscle rigidity; end-tidal partial pressure of carbon dioxide did not increase; and postoperative CK was normal. The patient was subsequently thought to have suf-

Table 2. Details of Malignant Hyperthermia-Susceptible Patients With Postoperative Pyrexia >38.5°C

Pt No.	Age	Reason for MHS label	Length of surgery (min)	Comments
1	5 mo	Second-degree relative, clinical diagnosis	Club-foot repair (140)	T-39.0°C 13 h postoperatively, treated with acetaminophen; RR, PR, and BP were 36–40 breaths/min, 140–180 beats/min, and 96–110 mm Hg, respectively, compared with preoperative values of 40–50 breaths/min, 130–140 beats/min, and 90–110 mm Hg, respectively
2	2 yr	Cousin, clinical diagnosis	Ptosis repair (100)	BP 195 mm Hg after 10 min of anesthesia (PR 170 beats/min). T <37.0°C intraoperatively, P_{ETCO_2} <40 mm Hg during IPPV, no rigidity. Postoperatively, BP remained 100–110 mm Hg, PR 90–120 beats/min and RR 20–30 breaths/min; T = 38.8°C at 3 and 9 h, settling on both occasions after oral acetaminophen
3	3 yr	Second-degree relative, positive biopsy	Nephrectomy for Wilm's tumor (240)	T-39.0°C at 2.5 h, associated with radiologic and clinical evidence of atelectasis; arterial blood gas analysis revealed no acidosis or hypercapnia
4	5 yr	Uncle, positive biopsy	Adenotonsillectomy (30)	T-39.0°C at 5.5 h and 38.9°C at 16 h; treated with acetaminophen. RR, PR, and BP were unchanged (20–22 breaths/min, 120–130 beats/min, and 100–118 mm Hg, respectively)
5	5 yr	Cousin, clinical diagnosis	Bronchoscopy after TEF repair (60)	T-38.8°C at 4 h, associated with radiologic and clinical evidence of atelectasis. Prophylactic dantrolene had been administered
6	5 yr	Second-degree relative, clinical diagnosis	Orchidopexy (65)	T-38.0°C at 6 h, 40.5°C at 8 h, and 38.0°C at 11 h, settling each time with acetaminophen. Arterial blood gas analysis revealed normal parameters; RR, PR, and PB were unchanged (22–30 breaths/min, 120–130 beats/min, and 110–120 mm Hg, respectively)
7	6 yr	Cousin, clinical diagnosis	Dental restoration (210)	T-38.9°C at 6 h. Clinical evidence of otitis media. RR, PR, and BP were unchanged (18–26 breaths/min, 104–130 beats/min, and 90–100 mm Hg, respectively). Prophylactic dantrolene had been administered
8	8 yr	First-degree relative, clinical diagnosis	Debridement of leg wound (150)	T-38.6°C at 4 h, treated with acetaminophen. Had persistent wound infections. RR, PR, and BP were unchanged (20–24 breaths/min, 90–120 beats/min, and 100–110 mm Hg, respectively)
9	9 yr	Previous MH reaction	Spinal fusion (205)	T-38.7°C at 19 h, treated with acetaminophen. RR, PR, and BP were unchanged (24–28 breaths/min, 110–130 beats/min, and 100–120 mm Hg, respectively). Prophylactic dantrolene had been administered
10	14 yr	First-degree relative, biopsy-positive	Spinal fusion (360)	T-39.0°C at 36 h, associated with radiologic and clinical evidence of atelectasis. Arterial blood gas analysis revealed normal acid-base parameters and carbon dioxide tension. Prophylactic dantrolene had been administered

Pt, patient; MHS, malignant hyperthermia-susceptible; T, temperature; RR, respiratory rate; PR, pulse rate; BP, systolic blood pressure; P_{ETCO_2}, end-tidal partial pressure of carbon dioxide; IPPV, intermittent positive-pressure ventilation; TEF, tracheoesophageal fistula; MH, malignant hyperthermia.

fered an adverse reaction to the contrast medium rather than to have had an MH reaction (12).

A 4-yr-old boy labeled MHS who had suffered a massive head injury required general anesthesia for craniotomy and died 2 days later without regaining consciousness. He exhibited no sign of MH throughout his hospital admission.

Discussion

In the past, overnight hospitalization of suspected or confirmed MHS patients after surgery has been a common practice, even after minor surgery. Previous to this review, these patients were admitted postoperatively for overnight monitoring at HSC. During our 10-yr study period, more than half the patients admitted postoperatively would have been eligible for same-day discharge if not for their MHS label. From the results of this large retrospective study, hospitalization of suspected or muscle-biopsy-proven MHS patients who have undergone uncomplicated surgery is not necessary.

None of the children with biopsy-proven MH in our study developed postoperative pyrexia or signs of MH after administration of nontriggering anesthesia. Postoperative pyrexia occurred in 10 (3.5%) suspected MHS patients. None of these children had an MH reaction nor were they given dantrolene. Postoperative pyrexia may have necessitated readmission of the three children who had outpatient-type procedures if they had been sent home on the day of surgery. All episodes of pyrexia responded to treatment with acetaminophen. Isolated pyrexia has been shown to be a poor predictor of MH in children (6); postoperative pyrexia is common in non-MHS children (13–15).

Postoperative MH reactions are rare after administration of anesthesia free of MH-triggering agents (5). Grinberg et al. (16) presented three cases of mild MH reactions developing in adult patients after trigger-free anesthetics. The reactions were diagnosed on the basis of pyrexia, moderate hypertension, mild metabolic acidosis, and slight hypercapnia. The longest interval between the completion of anesthesia and pyrexia was 5.5 h. Other factors, including a lack of postoperative analgesia, may have been involved. There have been no reports of severe MH reactions after trigger-free anesthesia. The period of risk after surgery of short duration with a trigger-free anesthetic technique is not known. After triggering anesthetics, most cases of postoperative MH have occurred within 1 h postoperatively (17–19), although one MH reaction was reported to have occurred 11 h after exposure to halothane (20). Recurrence after initial recovery from a fulminant MH reaction may occur >30 h postoperatively if dantrolene has not been given (21). The number of suspected MHS patients who have MH is unknown. Until an easy, reliable MH-susceptibility test is available, we will continue to use an MH protocol for suspected MHS children undergoing surgery.

Our findings suggest that intraoperative and postoperative complications are rare in patients labeled as MHS who undergo even prolonged surgery with trigger-free anesthesia. These are consistent with the findings of Hackl et al. (7) who reported a small postoperative increase in temperature and CK after 30 general anesthetic procedures in 24 biopsy-positive patients undergoing miscellaneous surgery with no other complications. As both this study and ours were retrospective, some complications may have been unrecorded in the patients' charts and thus missed. In addition, some MHS patients may have escaped inclusion in our survey. The number of confirmed MHS (as opposed to suspected MHS) patients is small (25 patients undergoing 33 procedures); however, our results suggest that the policy of admission of all MHS patients, regardless of the type of surgery they have undergone, may represent an unnecessary burden on health care resources. We conclude that same-day discharge for suspected or biopsy-proven MHS patients after uncomplicated ambulatory surgery is safe. A small number of these children may require readmission if a fever develops after discharge. A prospective study is now under way to investigate same-day discharge in children labeled MHS.

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Metoclopramide Reduces the Incidence of Vomiting After Tonsillectomy in Children

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The efficacy of intravenous metoclopramide in controlling vomiting in children after tonsillectomy was determined in a prospective randomized, double-blind investigation. One hundred two unpremedicated, ASA physical status I or II children between the ages of 1 and 15 yr who were undergoing surgical removal of the tonsils, with or without adenoidectomy, were studied. Anesthesia was induced either with halothane, nitrous oxide, and oxygen by mask or by intravenous thiopental and was maintained with halothane, nitrous oxide, oxygen, and intravenous morphine (0.1 mg/kg). Each child randomly received either 0.15 mg/kg of metoclopramide or saline solution placebo intravenously after transfer to the postanesthesia care unit. All episodes of vomiting were recorded for 24 h after completion of surgery. The incidence of vomiting in the saline solution group was 70%, compared with 47% in the metoclopramide group ($P = 0.026$). The authors conclude that the administration of intravenous metoclopramide in a dose of 0.15 mg/kg on arrival in the postanesthesia care unit significantly decreases the incidence of vomiting in children after tonsillectomy.

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Tonsillectomy, one of the most frequently performed surgical procedures in pediatric patients, is often performed as an outpatient procedure in some medical centers. Although postoperative bleeding is the most serious complication, vomiting is the most frequent (1,2). Persistent vomiting and poor oral fluid intake are leading causes of unscheduled overnight admission after ambulatory surgery (2). Metoclopramide has been shown to reduce postoperative vomiting in ambulatory pediatric strabismus patients; therefore, this study was designed to determine its efficacy as an antiemetic in children undergoing tonsillectomy (3).

Methods

The study was approved by the Human Studies Committee, and written, informed consent was obtained from the parents of 102 children, ASA physical status I or II, between the ages of 1 and 15 yr undergoing tonsillectomy with or without adenoidectomy. There was no history of motion sickness or other factor predisposing to postoperative vomiting in any patient enrolled in the study. Children were randomly assigned to a postoperative intravenous medication group, either metoclopramide (0.15 mg/kg) (group A) or sterile saline solution placebo (group B). All children were unpremedicated and had not ingested solid food or milk products after midnight on the evening before surgery. Ingestion of clear liquids was permitted until 6 h before the time of surgery.

Patients were transported to the operating room accompanied by one parent, and after placement of standard monitoring consisting of automated blood pressure cuff, pulse oximeter probe, electrocardiogram, and precordial stethoscope, anesthesia was induced. Younger patients received increasing concentrations of halothane, nitrous oxide, and oxygen delivered by mask, and older patients who consented to placement of an intravenous cannula while awake received thiopental followed by inhalation of halothane, nitrous oxide, and oxygen. Endotracheal intubation was accomplished in all patients without the aid of muscle relaxant so that reversal of neuromuscular blockade could be avoided, as the use of neostigmine is associated with an increased incidence of nausea and vomiting (4). Anesthesia was maintained with inhalation of halothane, nitrous oxide, and oxygen and intravenous morphine (0.1 mg/kg). After placement of an intravenous catheter, patients received lactated Ringer's solution in a volume to restore calculated fasting fluid deficit, deliver maintenance fluid for the duration of surgery, and compensate for measured blood loss. After removal of the tonsils was completed and hemostasis achieved, the

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Table 1. Clinical Characteristics of 102 Pediatric Patients Undergoing Tonsillectomy

	Saline solution (n = 51)	Metoclopramide (n = 51)
Age (yr)	6.5 ± 3.6	6.1 ± 3.4
Incidence of vomiting	70%	47%
No. of episodes of vomiting in patients who vomited	3.1 ± 2.4	1.1 ± 1.5
Time to first episode (postoperative h)	5.6 ± 2.5	6.4 ± 2.8

Results are mean ± SD.

stomach was decompressed by passing an orogastric tube under direct vision while the surgical mouth gag was still in place. After the trachea was extubated, patients were transferred to the postanesthesia care unit (PACU). Immediately on arrival at the PACU, each patient was given the coded intravenous study drug by a nurse who was unaware of the agent administered.

The time of drug administration was noted and recorded. All episodes of vomiting (nausea and retching were not included) that occurred both in the PACU and on the inpatient pediatric floor were timed and recorded by the nurse caring for the patient. No additional prophylactic antiemetic was administered. Oral fluid intake was not forced on patients, and children resumed oral intake voluntarily. The anesthesia, surgical, and nursing teams caring for these patients were unaware of the study drug given. Patients resumed oral fluid intake of their own accord. Fluids were offered and encouraged by the nursing staff; however, forced ingestion of a predetermined volume of oral fluid did not occur. All patients remained in the hospital for a minimum of 23 h and a maximum of 36 h after the completion of surgery.

The drug code was broken after all 102 investigations were completed. Statistical significance ($P < 0.05$) was determined with the Fisher exact test (two-tail), χ^2 analysis, and logistic regression.

Results

One hundred two patients were enrolled in the study, 51 patients in each group. The ages did not vary significantly between the two treatment groups. Posttonsillectomy vomiting occurred at a rate of 47% in the metoclopramide treatment group, compared with 70% in the saline solution placebo group (P = 0.026) (Table 1). In those children who did experience postoperative vomiting, the mean frequency was 1.1 ± 1.5 episodes in the metoclopramide-treated group compared with 3.1 ± 2.4 in the saline solution-treated group ($P < 0.001$) (Figure 1). Incidentally noted was the observation that patients >8 yr of age vomited less often than younger patients, regardless of treatment group. Vomiting occurred with a frequency of 29% in children >8 yr of age, compared with 68% in children <8 yr of age (P = 0.001). Alternatively, the effect of age and metoclopramide on vomiting are independent. In the younger children, <8 yr old, the metoclopramide-treated patients vomited at a rate of 53% compared with 82% in the saline solution placebo group (P = 0.014) (Table 2).

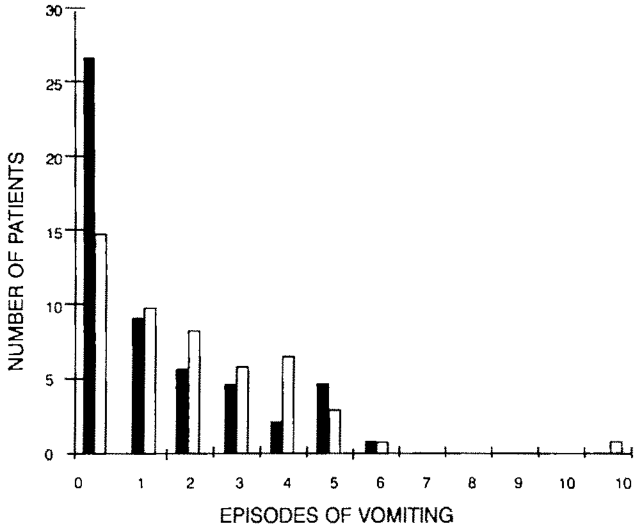

Figure 1. Frequency of postoperative vomiting in the two study groups (*solid bars*, metoclopramide; *open bars*, saline solution).

The two groups did not differ in the interval of time after surgery at which vomiting began. The first episode of vomiting occurred in the metoclopramide-treated patients at a mean of 6.4 ± 2.8 h after surgery compared with 5.6 ± 2.5 h in the placebo group ($P <$ 0.001) (Figure 2). The number of vomiting episodes occurring in the PACU and the inpatient unit did not differ between the two groups.

Discussion

The incidence of vomiting during the first 24-h period after tonsillectomy in unpremedicated children was found to be 70% in our patient population. The surgical literature reports the incidence of vomiting after tonsillectomy to range between 0.07% and 30.5% (1,2). It is difficult to determine the true incidence of vomiting in the pediatric tonsillectomy population, because studies vary in their definition of vomiting. The large discrepancy between our observations and those noted in the surgical literature is most likely due to criteria for reporting vomiting. Many authors do not include the first episode of

Table 2. Incidence of Vomiting in 102 Pediatric Patients Undergoing Tonsillectomy

	Metoclopramide (n = 51)	Saline solution (n = 51)	All patients	P value
Patients <8 yr old	21/39 (53.8%)	32/39 (82.1%)	53/78 (68%)	0.014
Patients >8 yr old	3/12 (25%)	4/12 (33.3%)	7/24 (29%)	NS
All patients	24/51 (47%)	36/51 (70%)	60/102 (58.8%)	0.026

NS, not significant.

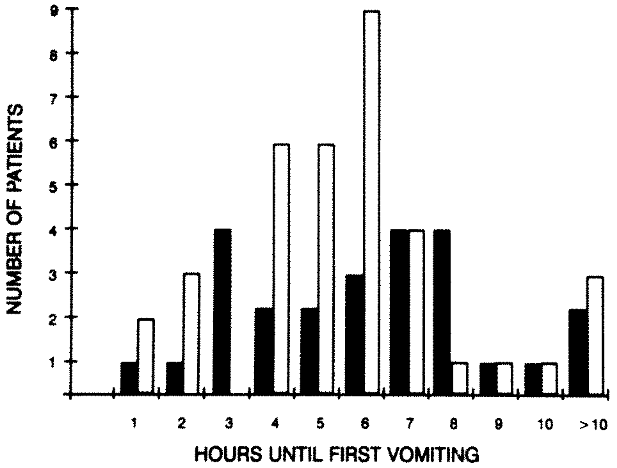

Figure 2. Onset of postoperative vomiting in the two study groups (*solid bars*, metoclopramide; *open bars*, saline solution).

vomiting, and others discount the second and third. Recurrent vomiting and poor oral fluid intake are dangerous, because they may lead to fluid depletion as well as add to the general postoperative discomfort experienced by children.

There is increasing pressure from insurance carriers to perform tonsillectomy exclusively as an outpatient procedure in an effort to stem the cost of rising health care (2). In view of this trend across the country, it is imperative that physicians caring for children search for solutions to the significant problem of postoperative vomiting and its potential for morbidity and unplanned overnight hospital admission.

Several antiemetic agents have been used postoperatively in children and studied, but none has been without significant undesirable effects. Intravenous droperidol in the effective dose of 0.075 mg/kg has been reported to decrease postoperative vomiting after strabismus surgery, but prolonged sedation associated with its use may delay discharge or result in unscheduled hospital admission (5,6). Other side effects associated with the use of droperidol in children include hypotension, restlessness, and extrapyramidal reactions that preclude it from routine administration (7). The use of lidocaine as an antiemetic in children has been studied, but the data on its effectiveness are conflicting and inconclusive (5,8).

Because of the effectiveness of metoclopramide in pediatric strabismus patients, the authors of this study chose to examine its effectiveness in reducing posttonsillectomy vomiting (3,9). Although the exact mechanism of posttonsillectomy vomiting is not well understood in children, anxiety, fear, or postoperative pain may play a role (10). It is known that patient gender, amount of intraoperative blood loss, performance of additional surgical procedures at the time of tonsillectomy, and surgical technique chosen are not predictive indicators of postoperative vomiting (2). We do know, however, that forcing early oral fluid intake on children after tonsillectomy does increase the risk of vomiting postoperatively (11).

The data presented in this study indicate that a difference in the incidence of vomiting between children >8 and <8 yr of age exists. The exact reason for this is not apparent, except that it is perhaps due to the older child's ability to suppress the vomiting reflex more effectively than the younger patient group. Intragastric blood either entering during the surgical procedure or postoperatively from an oozing tonsillar bed, as well as an altered gag reflex in the edematous postsurgical oropharynx, may possibly contribute to an increased stimulus to vomiting. An orogastric tube was passed intraoperatively under direct vision into the stomachs of all patients enrolled in this study in an attempt to evacuate a portion of blood and intragastric gas that may contribute to vomiting postoperatively.

The mechanism of action of metoclopramide is its ability to antagonize the inhibitory effects of dopamine on gastric smooth muscle, resulting in the forward propulsion of gastric contents. This may be uniquely beneficial in posttonsillectomy patients if in fact blood in the stomach is responsible for eliciting the vomiting reflex. Another mechanism by which the frequency of vomiting is decreased is by the action of metoclopramide in facilitating the release of acetylcholine from postganglionic nerve endings, resulting in increased lower esophageal sphincter tone.

As increased gastric emptying is not always correlated with therapeutic success, the central antiemetic effect of metoclopramide may be the most potent one. Apomorphine stimulation of dopamine receptors in the medullary chemoreceptor zone is known to result in nausea and vomiting, and metoclopramide is effective in blocking this response (12).

Although metoclopramide has been in use for a relatively short period of time, its side effects after a single dose are minimal. The marked somnolence seen with other agents is absent. Drowsiness has been reported in 10% of adult patients, but this has not been demonstrated in children. Extrapyramidal side effects have been reported in <1% of adult patients, and a study of pediatric oncology patients reported rare extrapyramidal side effects that were easily and readily reversed with the administration of diphenhydramine (3). Symptoms resembling parkinsonism have been reported in children, and these infrequent side effects are effectively treated with intramuscular diazepam (12). No side effects were noted in any patient enrolled in this investigation. It is important to note that our study provided for administration of a single prophylactic dose of metoclopramide, and this was not repeated; however, it remains to be seen whether the increased use of this drug will bring about additional reports of side effects in the pediatric population.

The dose of metoclopramide used in this study was determined by referring to data obtained in other patient populations. The dose of 0.15 mg/kg has been shown to be effective in decreasing gastric volume in healthy adult patients scheduled for elective surgery as well as those undergoing emergency procedures (13,14). In a study of prophylaxis against postoperative vomiting in pediatric strabismus patients, the lowest effective dose used was 0.15 mg/kg (3). The onset of action of intravenously administered metoclopramide is 3–5 min, and owing to the relatively short duration of action (2.4–4.6 h), it was administered immediately on arrival in the PACU to achieve the longest possible duration of action in the awake patient (3,13).

Morphine, in a uniform dose was administered to all patients to provide postoperative analgesia, even though opioids may contribute to postoperative nausea and vomiting. Morphine was chosen as the narcotic, because meperidine administration has been shown to increase the probability of vomiting in pediatric tonsillectomy patients (2).

On the basis of the results of our study, we recommend the use of intravenous metoclopramide in a dose of 0.15 mg/kg to control vomiting after tonsillectomy in children, especially those who are discharged on the day of surgery. Not only does administration of metoclopramide decrease the incidence of vomiting, but the severity is decreased when it does occur. The authors recognize that further investigation is warranted with regard to timing, dose, and administration. Perhaps a larger dose of metoclopramide may be effective in decreasing the incidence of vomiting further without increasing the incidence of significant side effects. As well, multiple dosing or drug administration preoperatively and intraoperatively may prove to be beneficial.

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Comparative Effects of Laryngeal Mask Airway and Endotracheal Tube Insertion on Intraocular Pressure in Children

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Intraocular pressure (IOP) measurements in children are frequently performed under halothane-nitrous oxide anesthesia; however, anesthesia face masks may limit access to the eyes, and tracheal intubation is associated with transient increases in IOP. Use of the laryngeal mask airway (LMA) permits the maintenance of a patent airway without the need for laryngoscopy and tracheal intubation. In a randomized study of 41 children, we compared the IOP, hemoglobin oxygen saturation, and hemodynamic responses to the insertion of an LMA or tracheal tube during a standardized steady-state anesthetic technique consisting of 1 MAC halothane and 66% nitrous oxide. Baseline measurements of IOP, hemoglobin oxygen saturation, heart rate, and arterial blood pressure were recorded and repeated within 15–30 s after insertion of the airway device and at 1-min intervals for 5 min. Insertion of the LMA required significantly less time (26 ± 16 vs 39 ± 17 s [mean ± SD]) and was associated with higher hemoglobin oxygen saturation values compared with the tracheal intubation. The LMA did not increase IOP, heart rate, or arterial blood pressure above baseline values. In contrast, tracheal intubation was associated with significant increases of IOP, heart rate, and arterial blood pressure. We concluded that the laryngeal mask offers advantages over tracheal intubation and the face mask for airway management in patients undergoing IOP measurements.

(Anesth Analg 1992;75:355–60)

Accurate, reliable intraocular pressure (IOP) measurements in children are difficult to perform without profound sedation or general anesthesia (1–3). A widely used technique involves the administration of halothane and nitrous oxide (N_2O) through a face mask; however, the anesthesiologist's attempts to maintain an adequate airway by manipulation of the jaw and face mask can occasionally interfere with the surgeon's ability to measure IOP. In addition, unrecognized pressure on the globe of the eye by the face mask may be a potential source of error. Although tracheal intubation will secure the airway and provide better conditions for the measurement, it is associated with an increase in IOP (3,4). The laryngeal mask airway (LMA) is a new device consisting of a cuff that forms a seal around the inlet of the larynx and a tube to direct gases to the larynx (Figure 1) (5–10). This method of maintaining airway control without tracheal intubation leaves the surgical field largely unobstructed and the anesthesiologist's hands free to perform other duties (5–9). However, data are not available on IOP changes when the LMA is used in children.

This prospective, randomized study was designed to compare the IOP and hemodynamic responses associated with the insertion of an LMA and an endotracheal tube in children during halothane-N_2O anesthesia.

Methods

After obtaining approval from the Washington University Human Studies Committee and written informed consent from the parents (or legal guardian) of the child, we studied 41 healthy ASA physical status I or II children scheduled for elective strabismus surgery. We excluded children <9 mo of age and <5 kg body wt, patients with poor lung compliance, those with a contraindication to the use of halothane and N_2O, and those in whom the use of the LMA would be unsuitable (e.g., children thought to have a "full stomach") (10).

Patients were asked to refrain from ingesting milk

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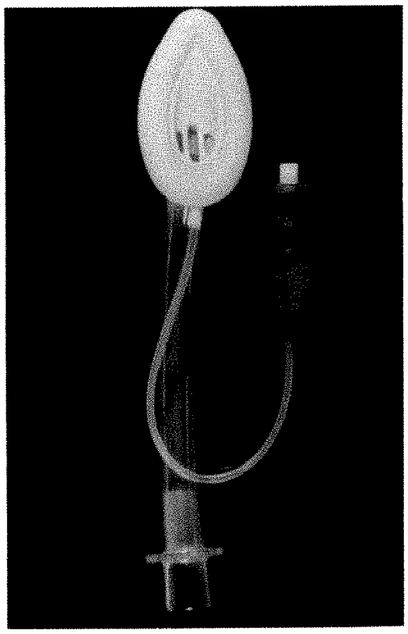

Figure 1. The pediatric laryngeal mask airway (size 2).

or solids for 6 h before induction of anesthesia but were permitted clear fluids until 2 h before the induction of anesthesia. No patient received preanesthetic medication. Anesthesia was induced in all patients with 0.5%–3% halothane and 66% N_2O in oxygen through a face mask. Inspired and expired gas samples were obtained from a catheter placed in the oropharynx and were analyzed by a mass spectrometer (Perkin-Elmer MGA 1100 mass spectrometer, Perkin-Elmer, Pomona, Calif.), calibrated with appropriate calibration gases (Scott Medical Products, Plumsteadville, Pa.). If the end-tidal nitrogen concentration exceeded 0.5%, the oropharyngeal catheter and the seal around the face mask were adjusted to exclude contamination of the sample by ambient air. Under these circumstances, the oropharyngeal samples have been shown to be representative of samples drawn from the distal end of the tracheal tube in children >6 mo of age and weighing >5 kg (11).

After loss of consciousness, the end-tidal N_2O concentration was kept constant at 66% in oxygen. In addition, all patients received halothane to maintain a constant end-tidal concentration that by itself was equivalent to 1 MAC for the patient's age (i.e., halothane end-tidal concentrations of 0.97% for 0.5–2.5 yr, 0.91% for 2.5–6 yr, and 0.87% for 7–11 yr). After vascular access was obtained, all patients received atropine (10 μg/kg) and atracurium (0.5 mg/kg) intravenously a minimum of 10 min before baseline measurements were made. The end-tidal CO_2 tension was maintained between 32 and 45 mm Hg with gentle positive pressure ventilation (peak inspiratory pressure <20 cm H_2O). Throughout the study, each patient was in the supine position, and the head was not elevated. Pressure on the eyes by the face mask was avoided at all study intervals.

After steady-state end-tidal gas concentrations for a minimal period of 10 min, baseline measurements of the IOP; heart rate (HR); systolic, diastolic, and mean arterial pressures; and hemoglobin oxygen saturation (Spo_2) were recorded. The HR, mean arterial blood pressure, temperature, and Spo_2 were measured by standard methods. The IOP was measured by one of two ophthalmologists with a Perkin's hand-held applanation tonometer after fluorescein was instilled in the conjunctival sac. Conditions for baseline and subsequent IOP measurements were evaluated by the ophthalmologist, who used a three-point scale: 1 = satisfactory, 2 = some difficulty, and 3 = unsatisfactory. During baseline IOP measurements, a Guedel oral airway was kept in place, a cushioned face mask (Vital Signs, Totowa, N.J.) was used, and the anesthesiologist's hands approached the patient's face from the side opposite to which the measurement was being made.

After baseline measurements were obtained, patients were randomized to a laryngeal mask (LMA) or an endotracheal tube (ET) group for airway maintenance. The time to insert the airway device (the time from removal of the face mask to connection of the anesthetic gas circuit to the airway device) was recorded, along with the lowest Spo_2 value during this period. Satisfactory placement of the airway device was confirmed by auscultation of the chest during gentle positive-pressure ventilation. The presence of bilateral equal breath sounds and good quality air entry excluded endobronchial intubation in the ET group and also excluded downfolding of the epiglottis over the laryngeal inlet with consequent airway obstruction in the LMA group.

The IOP and hemodynamic values were measured within 15–30 s of the insertion of the airway device and at 1-min intervals thereafter for 5 min, along with the Spo_2 values. After the airway was secured, patients continued to receive positive-pressure ventilation as previously described. After the study was completed, the choice of the airway device used during the strabismus correction surgery was left to the discretion of the attending anesthesiologist.

For purposes of statistical analysis, the IOP data were divided into sets relating to the left eye and the right eye, respectively, and separate analyses were performed with each data set. The IOP, Spo_2, and hemodynamic values after insertion of the airway device were compared with the preinsertion values by a one-factor analysis of variance for repeated measures, with separate evaluations for each airway management group. If the null hypothesis was re-

Table 1. Demographic Data and Baseline Hemodynamic and Intraocular Pressure Data in 41 Pediatric Patients Undergoing Elective Strabismus Surgery

	LMA group ($n = 21$)	ET group ($n = 20$)
Age (yr)	3.6 ± 3.4	4.5 ± 2.9
Weight (kg)	17.1 ± 13.3	17.7 ± 9.8
Gender (M/F)	9/12	12/8
ASA physical status (I/II)	18/3	17/3
Heart rate (beats/min)	144 ± 16	151 ± 13
Arterial blood pressure (mm Hg)		
Systolic	101 ± 11	105 ± 10
Diastolic	54 ± 16	56 ± 8
Mean	72 ± 13	77 ± 9
Baseline IOP (mm Hg)	13.3 ± 3.7	15.9 ± 3.0

Mean ± SD.
LMA, laryngeal mask airway; ET, endotracheal tube; M, male; F, female; IOP, intraocular pressure.

Table 2. Time for Insertion of the Laryngeal Mask Airway or Endotracheal Tube, Preinsertion and Postinsertion Oxygen Saturation Values, and Percent of Patients With Satisfactory Conditions for Measurement of Intraocular Pressure During Baseline and Subsequent Measurements in 41 Pediatric Patients

	LMA group	ET group
Time for insertion (s)	26 ± 16	39 ± 17[a]
Spo_2 values (%)		
Preinsertion	99.2 ± 1.1	99.8 ± 0.5
Postinsertion	98.8 ± 1.7	96.7 ± 4.0[a,b]
Satisfactory conditions during IOP measurements (%)		
Baseline (with face mask)	40	52
After airway device inserted	76[b]	75[b]

LMA, laryngeal mask airway; ET, endotracheal tube; Spo_2, oxygen saturation; IOP, intraocular pressure.
Mean ± SD.
[a] $P < 0.05$ vs LMA group.
[b] $P < 0.05$ vs preinsertion value.

jected, a Student-Newman-Keuls test was used for post hoc comparisons. At each time point of measurement, the IOP, Spo_2, and hemodynamic values between the two airway management groups were compared by an analysis of variance and by an unpaired Student's t-test, with Bonferroni corrections for multiple comparisons. A Wilcoxon signed rank test was used to compare conditions during baseline IOP measurements (when a face mask was used) with subsequent measurements made after the airway was secured. Where appropriate, Fisher's exact test or χ^2 tests with Yates' correction were used. A P value <0.05 was considered statistically significant. Values are presented as mean ± SD unless otherwise stated.

Results

There were no significant differences between the two groups in age, weight, gender, ASA physical status, or in the end-tidal gas concentrations at which the study was performed (Table 1). Because there were no significant differences in the IOP values between the two eyes of the same patient at any time in the analysis, we have arbitrarily chosen to present IOP values for the right eye only. This was the first eye in which IOP was measured at each time point. There were also no significant differences between the two groups in the baseline IOP, hemodynamic, or Spo_2 values.

Endobronchial intubation or downfolding of the epiglottis was not detected in any patient in the ET or LMA group, respectively. The time taken to insert a tracheal tube was significantly greater than the time taken to insert the LMA. The Spo_2 values immediately after the insertion of the airway device were significantly lower in the ET group compared with the LMA group (Table 2). However, after reinstitution of positive-pressure ventilation, there were no significant differences in the Spo_2 values between the two airway management groups.

Immediately after insertion of the airway device, there was a significant increase in IOP over baseline values in the ET group but not in the LMA group (Figure 2). During the entire study, IOP values in the LMA group were not significantly different from baseline values. In contrast, IOP values in the ET group remained significantly higher than baseline values (and higher than the corresponding values in the LMA group) for 2 min after tracheal intubation. By 3 min, there were no significant differences between the IOP values in the two groups or between the time-related IOP value and the baseline value in each of the two treatment groups (Figure 2).

Acute hemodynamic changes accompanied the changes in the IOP (Figure 2). Immediately after tracheal intubation there was a significant increase in HR and systolic, diastolic, and mean arterial pressures above baseline values and the corresponding values in the LMA group. In the ET group, HR remained significantly higher than baseline values for 4 min after tracheal intubation, whereas systolic, diastolic, and mean arterial blood pressures returned to baseline values in 3, 2, and 3 min, respectively. In contrast, there were no significant differences in HR, systolic, diastolic, and mean arterial pressures compared with baseline values in the LMA group (Figure 2).

Conditions for baseline and subsequent IOP measurements did not differ between the two airway management groups at any time point. However, satisfactory conditions were reported less often during baseline measurements when a face mask was

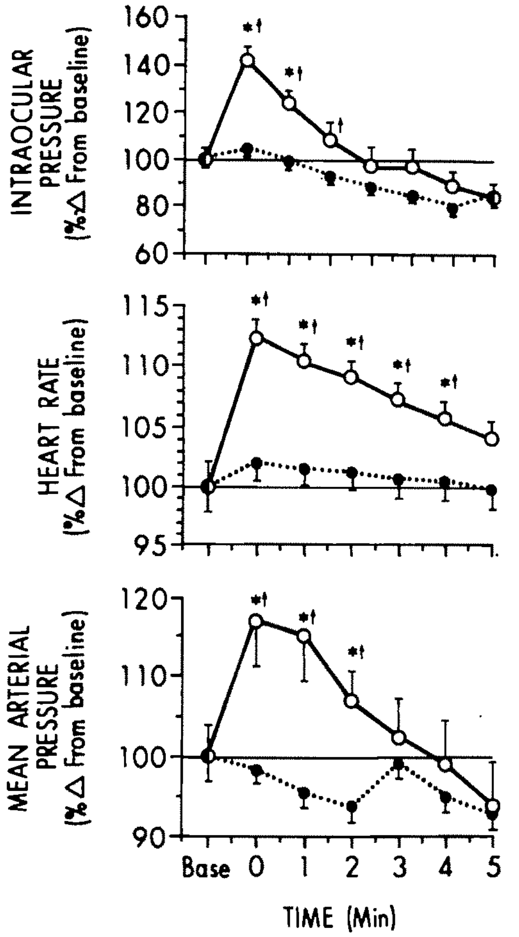

Figure 2. Comparison of the percent changes (%Δ) in intraocular pressure, heart rate, and mean arterial blood pressure over baseline (Base) values (100%) after the insertion of a laryngeal mask airway (●) or tracheal tube (○). Time zero is the time of insertion of the airway device. Error bars are ±SEM. *$P < 0.05$ versus baseline values. † $P < 0.05$ versus laryngeal mask group.

used than during subsequent measurements when the airway was secured with an ET or LMA (satisfactory condition noted in 46% during all baseline measurements vs 76% after the airway was secured; $P = 0.01$) (Table 2). The ophthalmologists considered the rapid and easy access to the eyes and the absence of movement of the surgical field to be major advantages of the LMA compared with conditions when a face mask was used. In the latter case, manipulations of the jaw and face mask required to maintain a patent airway interfered with IOP measurements.

Discussion

This study demonstrates that the use of the LMA provides better conditions for IOP measurements compared with a face mask and was not associated with IOP or hemodynamic changes. In contrast, tracheal intubation was associated with significant HR, systemic blood pressure, and intraocular pressure increases. This study also confirms our previous findings that the time-course of IOP changes after tracheal intubation are similar to the time-course of hemodynamic responses to tracheal intubation (2).

The mechanisms of IOP responses to tracheal intubation are uncertain. The acute changes in IOP are probably not simply responses to increases in arterial pressure. Although blood flow to the eye increases with tracheal intubation, the eye is capable of autoregulation of its blood supply (3,4). The increases in IOP associated with tracheal intubation may be secondary to increased sympathetic activity (4). Adrenergic stimulation may cause vasoconstriction and an increase in the central venous pressure, which has a closer relationship to IOP than systemic (arterial) pressure (4). In addition, adrenergic stimulation can produce an acute increase in IOP by increasing the resistance to the outflow of aqueous humor in the trabecular meshwork between the anterior chamber and Schlemm's canal (12).

Increased catecholamine and arterial blood pressure responses occur in adults who have undergone laryngoscopy without tracheal intubation (13). These data suggest that the major afferent source of the stimuli responsible for the adrenergic response may be the supraglottic, not the subglottic area. The supraglottic structures are distorted by the laryngoscope blade, whereas the subglottic area is stimulated after the tube passes through the vocal cords. Because inflation of the LMA cuff will cause some distortion of the pharynx and supraglottic structures, we would expect an acute adrenergic response to the insertion of the LMA in patients who are lightly anesthetized (9,14). Braude et al. (9) and Holden et al. (14) reported that hemodynamic and IOP responses, respectively, after the insertion of a LMA were attenuated compared with responses to tracheal intubation. However, we did not observe a significant hemodynamic or IOP response to the insertion of the LMA. Differences in the depth of anesthesia in our study and the previous studies may explain these differences (9,14). It is also possible that we missed the peak IOP response in some patients, because our measurements were made 15–30 s after placement of the airway device, and the peak response has been reported to occur at 20 s (14).

Holden et al. (14) recommended the use of the LMA for emergency intraocular surgery; however, in patients with penetrating eye injuries, the anesthesiologist must balance the risks of aspiration of gastric contents when the LMA is used against the risks of vitreous extrusion with increased IOP after tracheal intubation (2,4,10,14). The presence of the LMA in the hypopharynx may cause incompetence of the upper esophageal sphincter even with cricoid pressure (15). In addition, if the patient vomits, the lower portion of the laryngeal mask may prevent easy escape of the vomitus into the nose and oral passages, thereby directing it into the trachea (15,16). In acute eye injury cases, it may be safer to intubate the trachea after using pharmacologic agents (e.g., propofol, lidocaine, thiopental, opioid analgesics) to reduce IOP responses to tracheal intubation (4,17–20).

During our study, conditions were carefully controlled to ensure that factors other than insertion of the airway device were not responsible for changes in the IOP. For example, we used neuromuscular blocking agents to avoid increases in IOP associated with coughing or straining during insertion of the airway device. We also maintained a constant end-tidal concentration for ≥10 min to achieve comparable conditions between the two groups. Because the LMA is tolerated at a lighter depth of anesthesia than a tracheal tube (9), it may be possible to insert it without using neuromuscular blockade and perform IOP measurements even earlier than we reported in this study (6–8,10,21). In addition, insertion of the LMA is a technically simpler procedure than tracheal intubation (6–9,21) and is associated with a decreased risk for vocal cord trauma, which has been noted after even short periods of tracheal intubation (22).

Although the statistically significant differences in the time for insertion of a tracheal tube or LMA may not appear to be of clinical importance (39 vs 26 s), it may be possible to save 7–10 min of anesthesia time in children undergoing routine intraocular tension checks and examinations under anesthesia if the LMA is used rather than an endotracheal tube. Regardless of whether tracheal intubation is performed under deep halothane anesthesia or is facilitated by neuromuscular blockade, an additional 2–3 min is required to establish a satisfactory depth of anesthesia or adequate neuromuscular blockade, or both. In addition, the ophthalmologist will have to wait 3–4 min after tracheal intubation for the IOP to return to baseline values before a reliable measurement can be made (2). Extra time may also be required at the end of the procedure to antagonize residual neuromuscular blockade or eliminate halothane, or both, before the trachea can be extubated.

Although the differences in the oxygen saturation values between the two groups in our study were statistically significant, they were small, and no patient developed hypoxemia ($Spo_2 < 85\%$ for >15 s). However, a higher incidence of hypoxia was reported in a face mask group compared with a laryngeal mask group in children undergoing otological procedures (7). In that study and in our study, operative conditions were better with the use of the LMA compared with a face mask (7).

In conclusion, this study has shown that the insertion of an LMA during halothane-N_2O anesthesia in children is not associated with acute cardiovascular or intraocular pressure responses, whereas tracheal intubation is associated with increased HR, arterial blood pressure, and IOP. We would recommend the use of the LMA for routine IOP measurements in anesthetized children, because it provides better conditions for the measurements compared with a face mask and avoids the potential problems associated with tracheal intubation.

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Neuromuscular Pharmacology in Rat Neonates: Development of Responsiveness to Prototypic Blocking and Reversal Drugs

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The neonatal pharmacology of neuromuscular drugs was studied in vivo in newborn rats and in vitro in neonatal phrenic nerve-hemidiaphragm preparations. Drugs used to probe neuromuscular development in rat neonates were physostigmine, edrophonium, neostigmine, 4-aminopyridine, *d*-tubocurarine (dTc), and succinylcholine. The prejunctional actions of these drugs were monitored in relation to neonatal age by the appearance of stimulus-evoked repetitive discharge initiated by motor nerve endings and the occurrence and magnitude of the resulting enhancement of twitch tension. The occurrence and incidence of drug-induced fasciculations also served to track the development of functional motor nerve endings. Each of these prejunctional actions was inoperative until the third neonatal week, indicative of incomplete motor nerve development. In contrast, 4-aminopyridine, a nonanticholinesterase, evoked these prejunctional actions in 1-wk-old rat neonates. Neostigmine and edrophonium antagonized dTc as early as the first week; presumably, postsynaptic maturation had reached a functional level. 4-Aminopyridine also antagonized dTc at week 1. Rat neonates showed resistance to dTc blockade when tested by neonatal phrenic nerve-hemidiaphragm preparations in vitro. Relationships between age and 85%–95% transmission block declined to the adult level by week 5. This result indicates that in rat neonates, pharmacodynamic rather than pharmacokinetic mechanisms predominate in the development of responsiveness to dTc.

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The postnatal development of amphibian and mammalian neuromuscular junctions has been well defined (1–19). The structural and functional development of the rat neuromuscular junction achieves an adult level by the fifth postnatal week. The human neuromuscular junction exhibits an adult function and morphology by approximately the 12th postnatal week (3). This maturation process includes completion of myelination, disappearance of polyneuronal innervation, aggregation of postjunctional acetylcholine (ACh) receptors to form end plates, sensitivity to ACh, acetylcholinesterase (AChE) localization, and completion of functional and pharmacologic responsiveness (1,9–19).

Pharmacologically, however, classic neuromuscular drug effects have not been explored fully or quantitatively in either animal or human neonates. The present work reports and discusses the use of neonatal rat neuromuscular preparations in vivo and in vitro to study the pre- and postjunctional actions of *d*-tubocurarine (dTc), succinylcholine (SCh), neostigmine, edrophonium, physostigmine, and 4-aminopyridine (4-AP) on developing junctions. The principal aims were twofold: (a) to use well-defined pharmacologic probes in assessing developmental stages of mammalian neuromuscular junctions in vivo; and (b) to define the neonatal pharmacology of drugs having classical actions at neuromuscular junctions.

Methods

Rat pups aged 1–5 wk, born to Sprague-Dawley dams (Hill Top Farm, N.J.) were studied. All of the procedures used were in accord with AALAC guidelines. Dams in their last week of pregnancy were housed individually. Pup body weights were recorded at birth. These progressed from 10 to 50 g during the first three neonatal weeks. Pups were raised by their dams during the first three postnatal weeks. To ensure uniform nutritive conditions of the pups, the

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number of pups per dam was limited to 10 at birth, 7 at postnatal week 2, and 4 at postnatal week 3. The pups started eating on their own by postnatal day 17 or 18. The findings obtained in the rat neonates were compared with those from adult control Sprague-Dawley male and female rats, weighing between 200 and 250 g (i.e., >7 wk of age).

Pups and adults were anesthetized with 25% urethane solution intraperitoneally, 6 μL/g body wt for a body weight <100 g and 5 μL/g body wt for a weight >100 g. The anesthetized animal was secured on a polystyrene board, and an unobstructed airway was ensured by tracheostomy. A carotid artery was catheterized for intraarterial (IA) drug injection. The carotid arteries were the only blood vessels accessible for cannulation in 1-wk-old rat neonates.

Isometric muscle contraction was obtained as follows. A leg was immobilized by fixation of the knee and foot to the polystyrene board. A gastrocnemius muscle and its innervation were exposed in situ. The corresponding sciatic nerve was cut centrally. The gastrocnemius tendon was detached from its insertion and connected to a force transducer (model FT-3, Grass Instruments Co., Quincy, Mass.). The output from the transducer was amplified and recorded (transducer amplifier model 13-4218 and recorder model 220, Gould, Cleveland, Ohio). The exposed tissue was protected with paraffin oil and the preparation temperature thermostatically held at 37°C by radiant heat.

Indirect muscle contractions were evoked by supramaximal single stimuli applied to the sciatic nerve through a bipolar platinum electrode from a stimulator (model S-88, Grass Instruments Co.) via an isolation unit. For direct muscle stimulation, needle electrodes were inserted into the gastrocnemius muscle heads, and neural transmission was blocked by dTc. Both indirect and direct stimuli consisted of 0.1-ms square-wave pulses delivered every 4 s. Tetanic stimuli of 5–400 Hz were delivered for 30 s.

To record muscle fasciculations, the output from the transducer was amplified 10 times that for recording normal twitch tension. Nerve stimulation was discontinued when recording muscle fasciculations. Fasciculations, when these occurred, were observed in exposed muscle and in the intact animal. Their incidence was recorded with regard to age at the physostigmine doses shown in Table 1.

To record motor nerve ending* activity, thoracic and lumbar laminectomies exposed the S-1 and L-6 ventral roots; these contain gastrocnemius motor axons. In these experiments, the sciatic nerve was left intact. The S-1 and L-6 roots were disconnected at their origin from the spinal cord and separated into small filaments. A reactive filament was placed on bipolar platinum recording electrodes leading to differential preamplifiers (model AM 502, Tektronix, Beaverton, Ore.) and displayed on a storage oscilloscope (model 4072, Gould). Thus, prejunctional actions of gastrocnemius motor nerve terminals were monitored antidromically, as detailed by other studies from this laboratory (20–23).

Table 1. Percent Incidence of Physostigmine-Induced Fasciculation in Neonatal and Adult Rats

Dose[a] (mg/kg SC)	Postnatal week Week 2	Week 3	Week 4	Week 5	Adult
0.5	0	0	50.0	100.0	100.0
1.0	0	0	72.7	100.0	100.0
2.0	0	12.5	75.0	100.0	100.0
5.0	0	27.2	100.0	—	—
10.0	0	40.0	100.0	—	—

SC, subcutaneous.
[a] $n > 5$ for each subcutaneous dose.

Compound action potentials of gastrocnemius muscle, elicited by motor nerve stimulation, were recorded by bipolar platinum microelectrodes. The output was amplified through a differential preamplifier (model AM 502, Tektronix) and displayed simultaneously with the nerve action potentials on the storage oscilloscope described.

The drugs administered IA were edrophonium chloride, neostigmine bromide, dTc chloride, and SCh chloride; physostigmine sulfate was administered subcutaneously (SC). Atropine sulfate (2 mg/kg IP) was used to prevent muscarinic effects. All drugs were purchased from Sigma Chemical Co. (St. Louis, Mo.), and the solutions were prepared in 0.9% NaCl. Concentrations of each drug, with the exception of dTc and SCh, were prepared to limit injection volumes to 25 μL/10 g body wt for weights <40 g and to 50 μL/100 g body wt for weights >40 g. The dTc was prepared in 200- or 400-μg/mL concentrations; SCh was prepared in 1- or 2-mg/mL concentrations. The dTc and SCh were infused through a carotid artery at 15–20 μL/min with a microinjection pump (model CMA/100, Bioanalytical Systems, Lafayette, Ind.), and dTc or SCh was infused until an 80%–95% neuromuscular block resulted. The dTc or SCh doses required for this were calculated from the total volumes injected. During the dTc or SCh experiments, respiration was maintained by a rodent ventilator (model 683, Harvard Apparatus and Instruments, South Natick, Mass.).

At the end of all experiments, the animals were killed with sodium pentobarbital (>50 mg/kg IP).

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*Motor nerve endings include the distal Ranvier node, the myelinated axon leading to the unmyelinated nerve terminals, and the unmyelinated terminals.

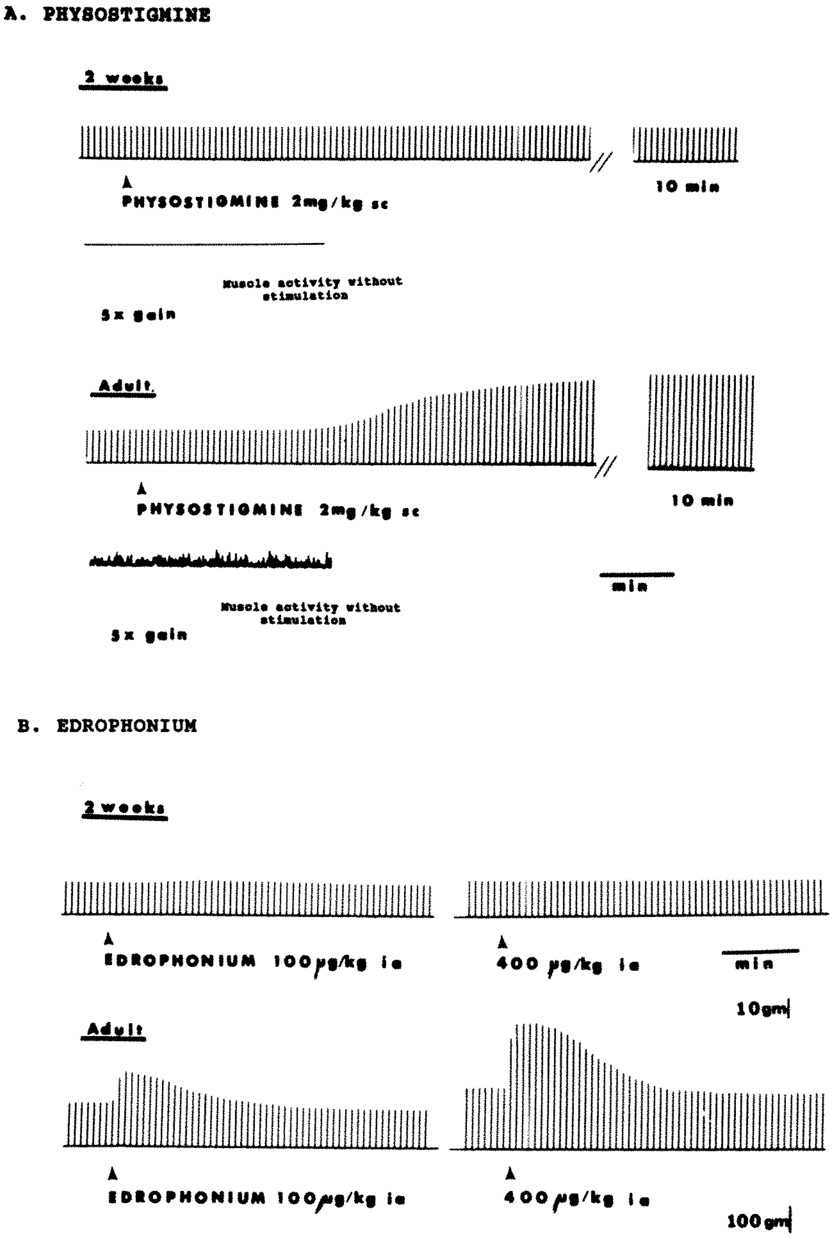

Figure 1. Physostigmine (**A**) and edrophonium (**B**) effects in a 2-wk-old rat neonate and an adult rat. Twitch potentiation and muscle fasciculation are absent in the rat neonate but are well-developed effects in the adult rat. In the drug-induced potentiations, the sciatic nerve was supramaximally stimulated at 0.25 Hz. Physostigmine and edrophonium injections are indicated by *arrows*. Muscle fasciculations were recorded in the absence of nerve stimulation and at a gain five times that used to record twitch tension. sc, subcutaneous; ia, intraarterial.

The neuromuscular blocking potency of dTc was studied in rat neonates of various ages, utilizing phrenic nerve-hemidiaphragm preparations in vitro. The muscle with its nerve was isolated and mounted in a Lucite chamber. The preparation was then bathed in Krebs' solution containing NaCl, 118 mM; KCl, 5 mM; $CaCl_2$, 2.5 mM; $NaHCO_3$, 30 mM; KH_2PO_4, 1 mM; $MgSO_4$, 1 mM; glucose, 11 mM. The pH was maintained at 7.4 when aerated with a mixture of 95% O_2 and 5% CO_2 (vol/vol%). The temperature of the bath was maintained at 36°C. The dTc concentrations studied were 1×10^{-6} and 1×10^{-5} M. The degree of neuromuscular block was calculated at the peak plateau effect of dTc; twitch tensions were measured before and after dTc and expressed as a percent block of twitch.

Statistical calculation for estimating group mean, standard error, and correlation coefficient was done by analysis of variance.

Results

Indirect Enhancement of Twitch Tension

Indirectly evoked twitch responses to the anticholinesterase drugs physostigmine and edrophonium are illustrated in Figure 1. The enhancement of

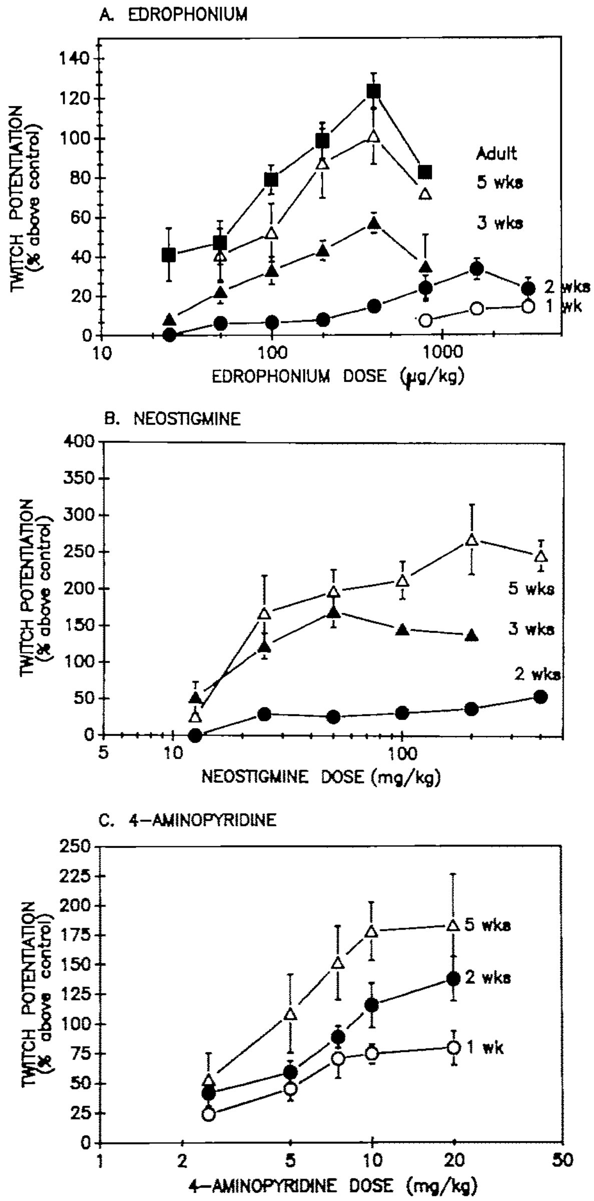

Figure 2. Dose- and age-related twitch potentiations plotted for intraarterial doses of edrophonium (A), neostigmine (B), and 4-aminopyridine (C). In all instances, sciatic nerve stimulation was supramaximal at 0.25 Hz. Maximal twitch potentiation (mean ± SE) is calculated as percent potentiation above control twitch. Each point represents the average of $n \geq 7$ experiments.

twitch tension (potentiation) caused by physostigmine, as seen in adult rats, was absent in 1- and 2-wk-old rat pups. Subcutaneous physostigmine doses as large as 10 mg/kg failed to produce potentiation in these rat neonates. By postnatal week 3, physostigmine potentiation appeared but was less than the response seen in the adult rat. The twitch potentiation evoked by edrophonium in the adult rats, like that of physostigmine, was absent in pups <3 wk old.

To determine whether the lack of potentiation in the 1–2-wk-old rat neonates is unique for these drugs, the nonanticholinesterase drug 4-AP was tested. Dose-twitch potentiation relationships, with respect to neonatal age, are plotted in Figure 2 for IA edrophonium, neostigmine, and 4-AP. These dose-range studies disclosed an insignificant twitch potentiation by neostigmine and edrophonium in the 2-wk-old rat pups compared with 3-wk-old pups and adults. The results of neostigmine were similar to those for physostigmine and edrophonium (Figures 1 and 2). At 3 wk and beyond, neostigmine and physostigmine twitch potentiations significantly exceeded those for edrophonium. In contrast to the threshold responses to physostigmine, edrophonium, and neostigmine with respect to enhancement of twitch tension in the 1- and 2-wk-old rat neonates, the threshold response of IA 4-AP was positive. The dose-response curves for edrophonium, neostigmine, and 4-AP in Figure 2 are seen to be dose and age dependent.

Actions on Neonatal Motor Nerve Endings

Neostigmine action on neonatal rat motor nerve terminals was investigated in 3-wk-old rat neonates given a 100-µg/kg dose IA. Figure 3 illustrates the repetitive action potentials recorded from ventral root fibers and a paired innervated muscle fiber after neostigmine dosing. As seen in Figure 3, repetitive motor nerve action potentials created a repetitive response in muscle. These events did not occur in 1- and 2-wk-old rat neonates.

In contrast to neostigmine, 4-AP in all 1- and 2-wk-old rat neonates tested caused both repetitive prejunctional firing (Figure 3) and significant twitch potentiation (Figure 2).

Drug-Induced Fasciculations

Rat neonates <2 wk old did not evidence physostigmine-induced fasciculations in doses as large as 10 mg/kg (Figure 1). In Table 1, the percent incidence of physostigmine fasciculations is tabulated with respect to dose and neonatal age. Rat neonates >3 wk old manifested a dose-related increase in the incidence of fasciculations. The adult rat response level was reached by week 5. Although not shown, the results with edrophonium and neostigmine did not differ.

Transmission Blocking Effects of Twitch-Potentiating Drugs

At large doses of edrophonium, transmission block occurred in rats ≥3 wk old (Figure 2). A threshold

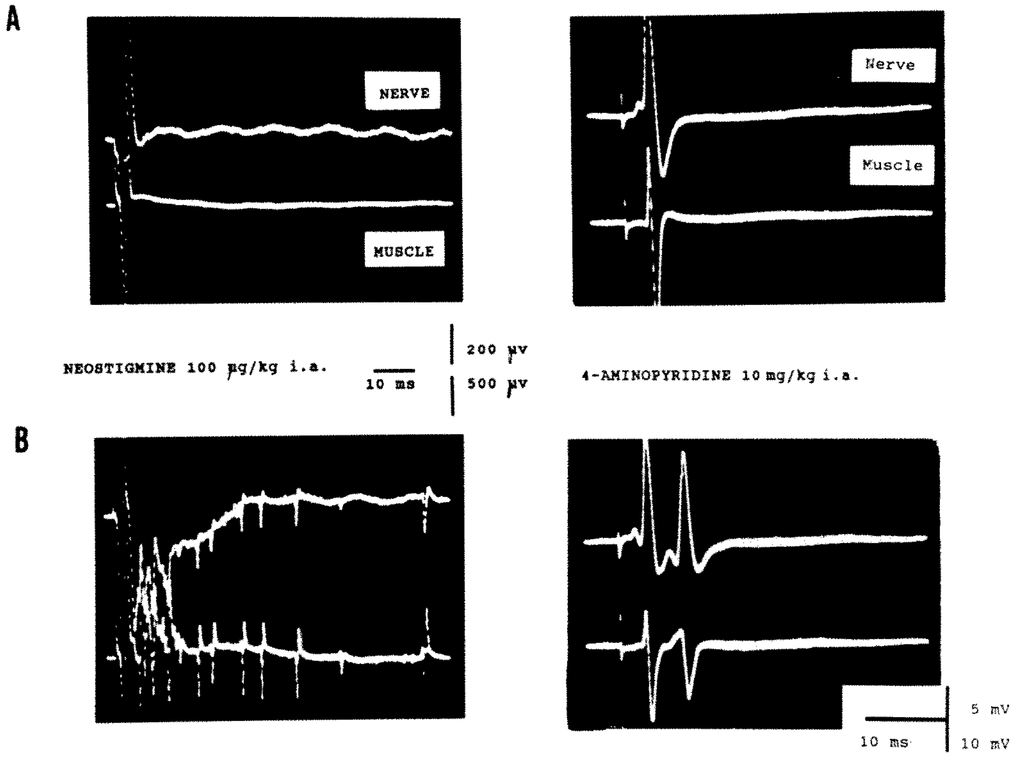

Figure 3. Neostigmine (*left*) and 4-aminopyridine (*right*) repetition induced in gastrocnemius motor nerve and muscle in a 3-wk-old rat neonate. Recordings were made from an innervating ventral root filament (S-1). *Top*: Nerve and muscle responses before drug administration. *Bottom*: Repetitive nerve and muscle action potentials recorded in response to single stimulation of the motor axon after intraarterial (i.a.) neostigmine (100 μg/kg) or 4-aminopyridine (10 mg/kg) injection. Correlation of the nerve and muscle events is evidenced by the fixed temporal relationship of their repetitive action potentials.

blocking action of neostigmine was visible in the 3-wk-old rat neonate; however, it could be increased at this point with larger neostigmine doses (not shown in Figure 2). A transmission blocking action did not occur with 4-AP.

Anticurare Action of Edrophonium and 4-Aminopyridine

To investigate the anti-dTc action of neostigmine, physostigmine, and edrophonium in the rat neonates, edrophonium was chosen as a prototype. Unlike the failure of edrophonium to potentiate twitch in 1- and 2-wk-old rat neonates, its anti-dTc action was demonstrable in the first neonatal week (Figure 4). The anti-dTc effectiveness of edrophonium increased with neonatal age and dose, as Figures 4 and 5A show. An adult response level was reached by week 5.

4-Aminopyridine antagonism of dTc was more effective than that of edrophonium (Figure 5B); 4-AP antagonized an 85%–95% dTc block completely in 1-wk-old rat neonates. The 4-AP anti-dTc efficacy was dose and age related (Figure 5B). Furthermore, 4-AP antagonism not only fully restored dTc-depressed twitch responses, but also potentiated twitch amplitude above the pre-dTc level. This occurred in relation to dose at all ages.

Responses to D*-Tubocurarine and Succinylcholine*

The dTc and SCh doses needed to produce an 80%–95% twitch block were calculated from the total volume of dTc or SCh infused and the body weight of the rat pup. Doses of dTc and SCh producing an equivalent level of neuromuscular block depended on neonatal age and body weight as a correlate of age. In pups <3 wk old, the average dose of either dTc or SCh needed to produce 80%–95% neuromuscular block was much larger than that for adult rats. The results are plotted in Figure 6. Figure 6A correlates the dTc doses necessary for 80%–95% block with the individual neonatal body weights as well as the average body weight for each age group. The correlation coefficients for the linear log-log plot of dTc dose versus body weights and ages was $r = -0.918$ ($P < 0.05$). Succinylcholine was studied in relation to rat neonatal body weight (Figure 6B), assuming neo-

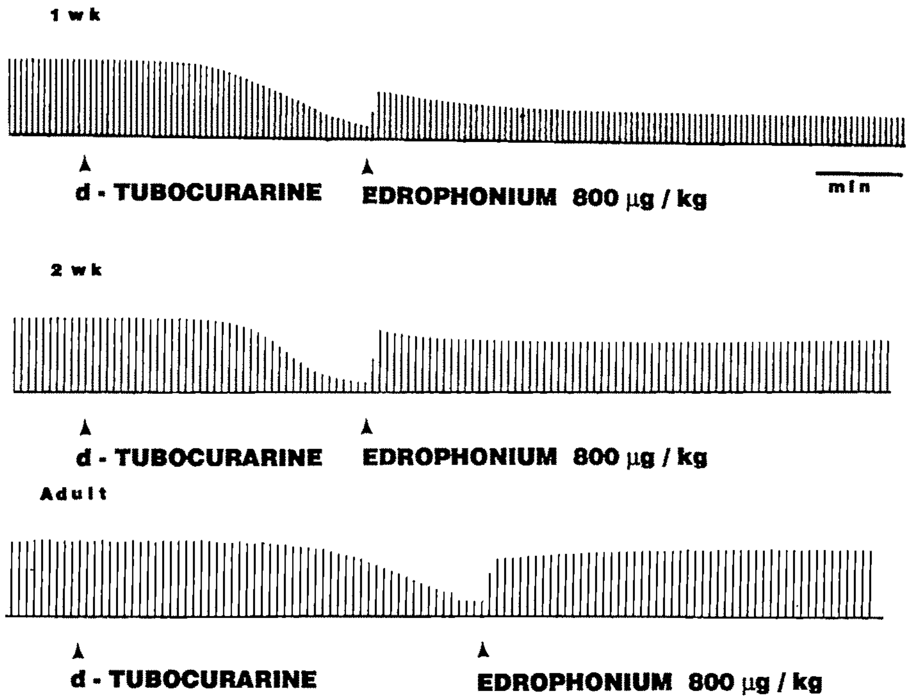

Figure 4. Anti-*d*-tubocurarine effect of edrophonium in rat neonates (1 and 2 wk) and in an adult rat. Twitch responses to single supramaximal stimulation of a sciatic nerve at 0.25 Hz. *d*-Tubocurarine was infused to produce 85%–95% neuromuscular block. Edrophonium (800 μg/kg) was injected intraarterially (*arrow*) when block reached its peak.

natal body weight to be a correlate of neonatal age. As Figure 6 indicates, the correlation coefficient in this case (Figure 6B) was $r = -0.916$ ($P < 0.05$). The dTc dose for 80%–95% block in adult rats was attained by the fifth neonatal week. The SCh dose for 80%–95% block in adult rats, like that for dTc, was reached in an estimated 5 wk.

Figure 7 shows the dose-age neuromuscular blocking effects of dTc on phrenic nerve-hemidiaphragm muscle preparations in vitro. As shown in Figure 7, the dTc blocking effect was age related. At 10^{-6} M, dTc did not cause neuromuscular block in 1- and 2-wk-old rat neonates; however, this concentration did produce an 89% block in 4-wk-old rat neonates. A 10-fold increase in dTc concentration (10^{-5} M) produced only a 25% block in 1-wk-old rat neonates but caused complete block in those >3 wk old. This approximated a 20-fold dTc sensitivity difference between 1- and 4-wk-old rat neonates.

Discussion

The failure of 1–2-wk-old rat neonates to generate neural repetitive firing and twitch potentiation after the administration of physostigmine, neostigmine, or edrophonium up to doses 65 times those that are effective for the adult rat points to an incomplete development of motor nerve endings at these ages. In classical studies, Standaert (20,21) showed conclusively that twitch potentiation of this type results from the generation of repetitive discharging by mammalian motor nerve endings and its transmission to muscle (see Figure 3). This sequence converts the muscle response to each single nerve stimulus to a tetanic form of contraction. This has since been confirmed in other studies (24–36).

Twitch potentiation is a simple but accurate measure of neural repetitive activity in that the whole muscle serves to integrate the total activity transmitted. Consequently, the absence of drug-induced twitch potentiation in the 1–3-wk-old rat neonate points to an incomplete development of motor nerve endings. This was confirmed by the experiments in which motor nerve endings were monitored for generation of repetitive activity; the lack of such activity paralleled the absence of twitch potentiation. Repetitive generation and twitch potentiation appeared by week 3, increasing progressively to an adult level by week 5.

The absence of repetitive firing and twitch potentiation in the 1–3-wk-old rat neonates points to an incomplete myelination. This accords with the morphologic findings of Webster (1) and Redfern (10). Because the triggering of repetitive activity in motor axons requires an interaction between their unmyelinated terminals and the corresponding distal Ranvier nodes (Figure 8), myelination between node and the origin of the unmyelinated terminals is necessary.

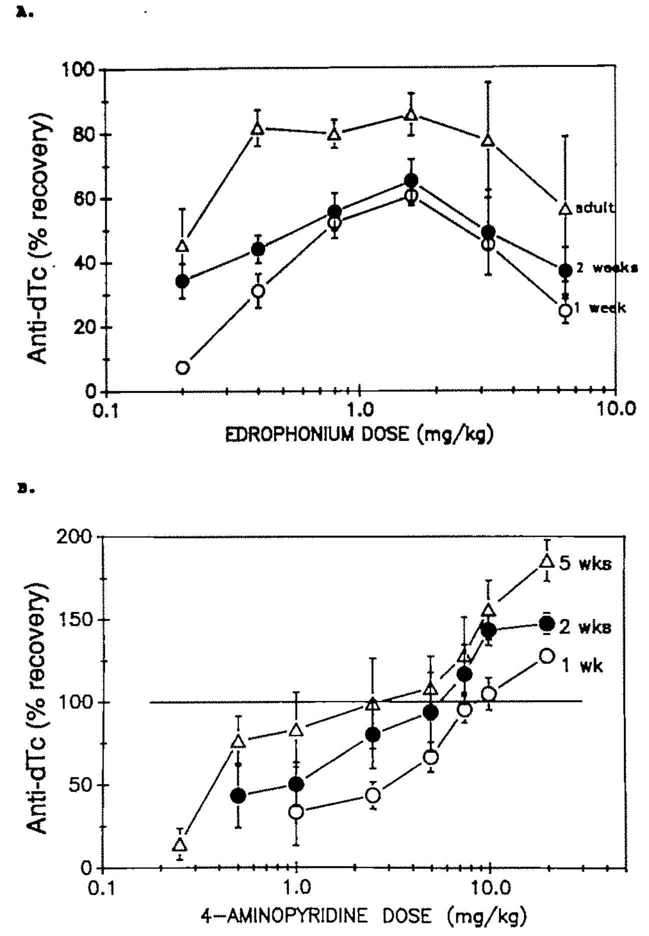

Figure 5. Dose-anti-dTc and age relationships are plotted for edrophonium (A) and 4-aminopyridine (B). The dTc was infused intraarterially to produce 85%–95% neuromuscular block before edrophonium or 4-aminopyridine administration. Peak recovery from dTc block (mean ± SE) calculated as percent recovery from maximal twitch depression. Each point represents the average of $n \geq 7$ experiments.

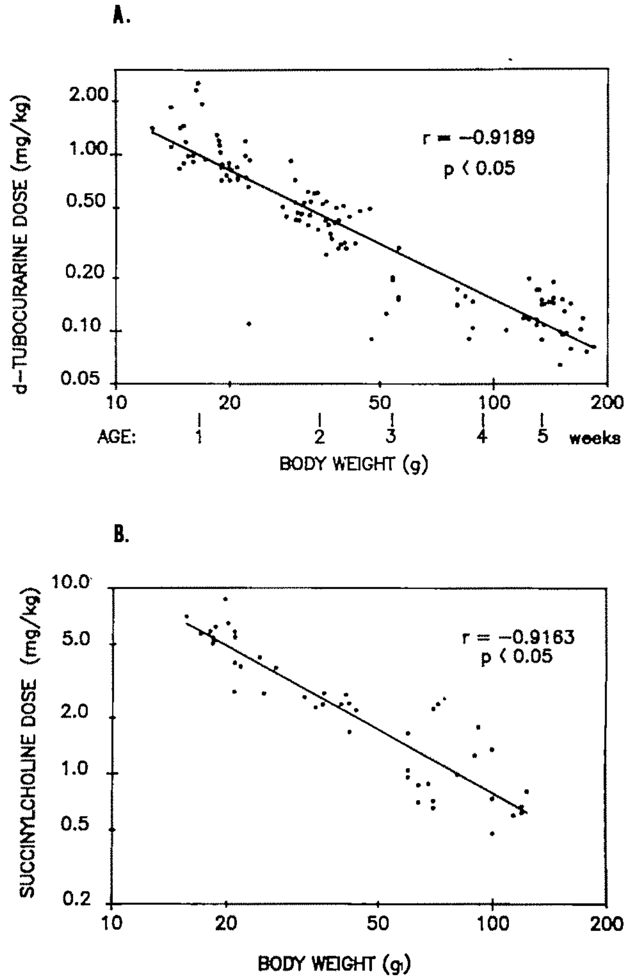

Figure 6. (A) Relationships between rat neonatal age and body weights and log *d*-tubocurarine doses (infused intraarterially) required to produce 85%–95% neuromuscular block. (B) Log succinylcholine doses (infused intraarterially) required to produce 85%–95% neuromuscular block in relation to rat neonatal body weights.

Neostigmine, edrophonium, or physostigmine alters the excitability properties of the unmyelinated terminals such that after their invasion by a single impulse, a prolonged depolarization follows (20,21,24–29,32,34,35,37–40). As Figure 8 depicts, the depolarized terminals serve as a long-lasting cathodal focus for reexcitation of the distal axonal nodes. Thus, a persisting motor nerve terminal depolarization must be at or above its distal node's threshold level for reexcitation (repetitive generation).

Further, an appropriate development of the unmyelinated nerve terminals per se must be attained if repetitive firing and twitch potentiation are to be evoked by physostigmine or related drugs. The need for intact unmyelinated nerve terminals is evidenced by the loss of a repetitive firing capacity after injury by certain neurotoxins that damage them (41–44). In this context, incomplete development of the motor nerve terminals per se in the 1–3-wk-old rat neonates probably contributes to their failure to generate repetitive firing and twitch potentiation.

In the 1–2-wk-old rat neonate, it may be that certain ion channels in their motor nerve terminals, requisite for the generation of repetitive firing, await development. Because calcium channel blockers, such as the metal ions Mg^{2+}, La^{3+}, Cd^{2+}, Co^{2+}, Ni^{2+}, or Mn^{2+}, antagonize the repetitive generating action of physostigmine and related drugs (45), it appears that these drugs act on at least one of the diverse calcium ion channels ubiquitous in excitable cells and nerve terminals (46–48). Brigant and Mallart (49) have demonstrated calcium channel(s) in the unmyelinated motor nerve terminals of the adult mouse.

A calcium channel activation required for repetitive firing may be that discussed by Tsien (47) and Tsien et al. (48). This channel, identified in central

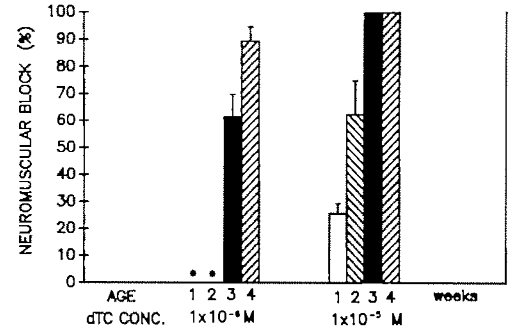

Figure 7. Effects of dTc on isolated phrenic nerve-hemidiaphragm muscle preparations in vitro in 1-, 2-, 3-, and 4-wk-old rat neonates. Mean dTc twitch block (±SE) calculated as a percent block of the control twitch before dTc. The two *bar groups* indicate the average blocking responses to 1 × 10^{-6} M dTc (*left*) and to 1 × 10^{-5} M dTc (*right*). *Asterisks* indicate zero block. *Solid and hatched bars* represent responses of 3- and 4-wk-old rat neonates at each of the two dTc concentrations tested. *Right-hand bars*: *open bar* shows response to 1 × 10^{-5} M dTc in 1-wk-old rat neonate; *hatched* (▨) *bar* shows response to 1 × 10^{-5} M dTc in 2-wk-old rat neonate. Each bar represents the average of $n \geq 5$ experiments.

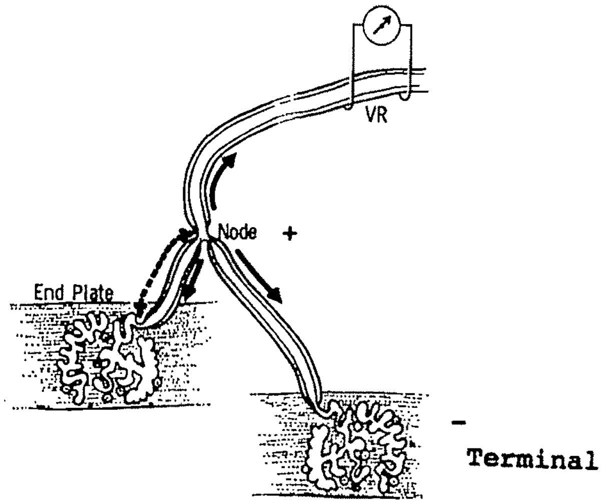

Figure 8. Mechanism of repetitive generation by motor nerve endings. Administration of an anticholinesterase drug, followed by single stimulation of the axon causes the unmyelinated terminals to develop a sustained depolarization (−); the unaltered distal axonal node returns quickly to its resting level, becoming electropositive (+) to the terminals. Current flow from positive source to negative sink (*dashed line*) reexcites the axon. Repetitive excitation recurs as long as the terminals remain sufficiently depolarized to enable current flow at a threshold for nodal excitation. Repetitive bursting is reinitiated with each single stimulus as long as the drug in the junction is at an effective level. Repetitive action potentials recorded from ventral root (VR) axons reflect this generating capacity of normal adult unmyelinated terminals (see Figure 3). (Adapted, with permission, from the *Annual Review of Pharmacology*, Volume 9, © 1969, by Annual Reviews, Inc.).

neurons and squid nerve terminals, is voltage dependent and inactivates slowly (half-life approximately 1 s). This behavior would provide a plateaued nerve terminal action potential appropriate for the generation of repetitive firing (cf. Figure 8). Conceivably, if such is the case, a putative calcium channel required for the generation of repetitive firing by physostigminelike drugs is undeveloped in the unmyelinated terminals of the 1–3-wk-old rat neonates.

Full manifestation of contractile potentiation in rat neonates at weeks 3–5 may be impaired by conduction block at branch points of unmyelinated intramuscular nerve fibers. At these points, the safety factor for conduction is reduced. This has been demonstrated in various unmyelinated nerve fibers and shown to be intensified by repetitive impulses (50,51). Although the earliest rat neonate is able to conduct and transmit single impulses, its well-known inability to maintain an indirect tetanus (3) probably contributes to conduction blocks in intramuscular nerves. Also contributory to decay of indirect tetanic maintenance are the neonatal polyneuronal innervation, incomplete myelination, and a minimal reserve in neonatal rat terminals. In view of these circumstances, failure of tetanic maintenance would be more pronounced in the first 2 wk of life.

Neostigmine and like drugs, as well as certain cholinergic agonists such as SCh (53), when administered to humans or intact animals in adequate doses, cause fasciculations that are generated by motor nerve endings, as first demonstrated for SCh by Standaert and Adams (53). This has since been confirmed (54,55). Fasciculations caused by ACh are similarly generated (28). Such drug-induced fasciculations are spontaneous discharges involving the same mechanism as that described for stimulus-dependent repetitive firings (Figure 8). Consequently, fasciculations are absent in the 1- and 2-wk-old rat neonate in which myelination is incomplete, but with the completion of myelination, fasciculations appear in 3-wk-old rat neonates and increase in intensity to an adult level by week 5. Thus, fasciculations, stimulus-dependent repetitive generation, twitch potentiation, and the completion of myelination concur in development in 3–5-wk-old rat neonates. These findings are commensurate with clinical reports describing little or no fasciculations in human neonates and infants after administration of SCh (7,56). Although SCh is not an anti-AChE, it has been shown to cause repetitive firing by adult motor nerve endings like that produced by physostigmine and related drugs (53,54).

4-Aminopyridine is a specific potassium channel blocker in both myelinated and unmyelinated axons and is not an anti-AChE (57). This drug differed sharply from the physostigminelike drugs in that 4-AP caused twitch potentiation, repetitive firing, and fasciculations in the 1–3-wk-old rat neonates. These effects in the youngest rat neonates appeared no different from those produced by the physostigmine-type drugs in the older rat neonates.

4-Aminopyridine when applied to axons including motor axons elicits repetitive firing (58,59). We propose that such 4-AP action on neonatal motor nerve axons, at both intra- and extramuscular sites, accounts for the twitch potentiation, repetitive firing, and fasciculation seen in the 1–5-wk-old rat neonates. This 4-AP action is attributable to blockade of neural potassium channels and thus to prolonged action potentials at these sites, leading to axonal repetitive firing (57).

In several species, 4-AP potentiates skeletal muscle contraction, in part due to block of muscle fiber potassium channels (57); however, in our studies, the failure of 4-AP to increase twitch tension responses in dTc-blocked muscle, directly stimulated, indicates that a 4-AP action on muscle probably does not account for the indirect twitch potentiation seen in the 1–5-wk-old rat neonates. In unpublished experiments, we have observed regularly that 4-AP produces neural repetitive discharge in the presence of 80%–90% dTc blockade. This happens in conjunction with dTc antagonism, continuing after a point of full recovery such that twitch potentiation follows. This is not seen with the neostigmine-type reversal drugs.

A number of studies (45,57,60) have demonstrated the anti-dTc action of 4-AP. Because of prolonged block of neural potassium channels by 4-AP, depolarization is maintained. During this period, calcium entry occurs. This event in the unmyelinated nerve terminals increases transmitter release (61,62), which in turn is considered to be the primary mechanism by which dTc and other nondepolarizing blockers are antagonized competitively. Because the neuromuscular transmitting system is functional in the 1-wk-old rat neonate, 4-AP was seen as an effective dTc antagonist.

The antagonism of dTc block in the 1-wk-old rat neonates by physostigmine and related drugs, as illustrated herein by edrophonium, is most simply explained by their anti-AChE action and transmitter accumulation in the primary cleft, leading to competitive antagonism of dTc. In this respect, the ultimate consequence of dTc antagonism by the anti-AChE drugs and 4-AP in the 1–5-wk-old rat neonates is the same.

Adult rats and humans differ only quantitatively in their pharmacodynamic responses to the drugs used in this study. The principal quantitative difference is the greater sensitivity of the adult rat to dTc and SCh compared with humans (63).

In both rat and human neonates, the requirement for SCh and dTc blockade is greater than in the adult (64–69). The rat neonate is exceptionally resistant to dTc block, as our studies demonstrate. This seems not to be the case in human neonates (70–72). Apart from this large quantitative difference, the pharmacodynamic responses of neonatal and adult rats are qualitatively like those in humans.

The discovery in rat neonates of a strong negative correlation for both dTc and SCh blocks (Figure 6) as functions of weight and age reveals another aspect of neonatal neuromuscular pharmacology. Resistance to SCh block in human infants was demonstrated by Stead (64) and has since been confirmed by others (56,64–68). It was considered that a larger volume of distribution in infants versus adults might explain an apparent resistance to SCh block (69,73); however, the need of some infants for SCh infusion rates three to four times that for others suggests that a pharmacodynamic component must be considered as well as a pharmacokinetic difference (56).

There is still no known explanation for the neonatal resistance to SCh. The increased requirement for SCh in blocking transmission in neonates may relate to polyneural innervation. These junctions are weakly functional and precede the formation of the single, mature junctions readily susceptible to the excitatory and blocking actions of SCh. Polyneuronal innervation may therefore be a principal factor in neonatal resistance to SCh actions.

Whether the dTc age-related resistance found in neonatal rats applies to human infants is uncertain (7,70,74). Matteo et al. (71) observed that the effective dTc dose for infants was threefold that required for an average child. They suggested that this may result from the retention of fetal ACh receptors.

For dTc, drug distribution volume may be thought to explain the larger doses required for block in rat neonates. Fisher et al. (72) found the steady-state distribution volume of this drug in humans in the following order: neonates > children > adults. Matteo et al. (71), however, found that resistance to dTc in infants cannot be explained entirely by distributional differences. In the present study, distributional differences do not offer a convincing explanation for the neonatal resistance to dTc. The 10-fold higher dose needed to produce a block in 1-wk-old rats (Figure 6) is 10 times greater than estimated neonatal distribution volumes. At most, the apparent volume of distribution in the youngest neonates is approximately five to six times that for the adult.

For the rat neonate, the studies of dTc block in a phrenic nerve-hemidiaphragm preparation in vitro apparently resolves this issue (Figure 7). The striking resistance of rat neonates to dTc and the gradual decrease of resistance with age were found in the in vitro neuromuscular system, just as these were seen in the in vivo preparations. In the in vitro preparations, distribution volume is not a factor. Thus, the strong resistance to dTc in rat neonates is chiefly pharmacodynamic and less likely pharmacokinetic. This points to an ongoing development of postjunctional receptor-ionophores during the first month of life in the rat neonate.

The large requirement of rat neonates (1–5 wk) for dTc and SCh block points to an incomplete development of postjunctional cholinoceptors. Presumably, the receptor binding affinity for these drugs is weak and readily dissociable. In this circumstance, the high concentrations of dTc and SCh necessary for block in the rat neonates may have also hindered edrophonium reversal.

The pharmacologic actions of the drugs used to probe the neuromuscular junctions of neonatal rats furnish further insight into the pharmacodynamic and temporal aspects of neuromuscular development.

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Epidural Test Dose and Intravascular Injection in Obstetrics: Sensitivity, Specificity, and Lowest Effective Dose

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The authors studied the sensitivity and specificity of several epidural test doses as markers of intravascular injection in laboring patients in a prospective double-blind, randomized study. Fifty-nine parturients were assigned randomly to receive an intravenous injection of either normal saline solution (3 mL, NS group) or 1.5% lidocaine with epinephrine 1:200,000 (1 mL, EPI-5 group; 2 mL, EPI-10 group; or 3 mL, EPI-15 group). The EPI-5 and EPI-10 doses were diluted to 3 mL volume with normal saline solution. All injections were given during uterine diastole. Maternal heart rate was monitored with a pulse oximeter. An observer who was unaware of the study treatment recorded the baseline and the peak maternal heart rate within the first minute after the injection and questioned the patient about tinnitus, dizziness, metallic taste, and palpitations. He then recorded his opinion as to whether the patient had received the saline or the test solution. Analysis of the maternal heart rate showed an average increase (baseline-to-peak criterion) of 8 ± 10 beats/min (mean ± SD) in the NS group. In the other groups, the increase was 21 ± 8 (EPI-5 group), 31.5 ± 13 (EPI-10 group), and 29 ± 9 beats/min (EPI-15 group). A baseline-to-peak criterion of >10 beats/min identified all intravascular injections in the EPI-15 (by design) and EPI-10 groups (15 of 15 and 14 of 14, respectively) with a sensitivity of 100%. Specificity was 73% (11 of 15 true negatives). The calculated areas under the receiving operating characteristic curves for the EPI-5, EPI-10, and EPI-15 groups were, respectively, 0.83 ± 0.8 (SE), 0.91 ± 0.5, and 0.93 ± 0.5. For the EPI-10 and EPI-15 groups, positive predictive value (+PV) ranged from 24% to 41% (assuming a prevalence between 8% and 16%). The negative predictive value (−PV) was 100%. The observer also correctly guessed the treatment of all patients in the EPI-10 and EPI-15 groups. Thus, the sensitivity was 100%, whereas the specificity reached 93% (14 of 15 true negatives). For the observer, the positive predictive value was 55%–73% and the negative predictive value 100%. Analysis of the symptoms (alone and in combination) exhibited low sensitivity (<67%). We conclude that (a) a test dose containing either 10 or 15 μg of epinephrine is 100% sensitive as a marker of intravascular injection (area under the receiving operating characteristic curves 0.91–0.93 and negative predictive value 100%); (b) the positive predictive value of this technique may range between 55% and 73%; and (c) 27%–45% of epidural catheters may be unnecessarily removed in the presence of a positive test.

(Anesth Analg 1992;75:372–6)

The use of 15 μg of epinephrine in the epidural test dose (ETD) as a marker of intravascular injection was first described by Moore and Batra (1). Their study showed an increase in mean heart rate of approximately 30 beats/min in healthy nonpregnant volunteers after an intravenous injection of 15 μg of epinephrine. Since then, the use of epinephrine as a component of an ETD has been widespread.

In 1990, Guinard et al. (2) determined the sensitivity of an epinephrine-containing ETD, as well as its lowest effective dose in healthy nonpregnant volunteers. They concluded that 10 μg of epinephrine is the lowest effective dose and that the agent is 100% sensitive in detecting intravascular injection; however, the efficacy of an epinephrine-containing ETD used to detect intravascular injection in laboring patients has been questioned because of the wide variability in maternal heart rate (MHR) (3).

We designed this study to assess the sensitivity and specificity of an epinephrine-containing ETD in laboring patients, as well as its lowest effective dose in detecting an unintentional intravascular injection.

Methods

This study was approved by the Institutional Human Research Committee, and informed written consent

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was obtained from each subject. Fifty-nine laboring, unmedicated women (cervical dilatation >4 cm, uterine contractions at $\leq$3–4-min intervals) were enrolled in the study after they requested lumbar epidural analgesia. Their ASA physical status was I or II after an uncomplicated pregnancy. Patients with a history of hypertension of any etiology were excluded. The MHR was continuously monitored with a pulse oximeter (Nellcor, Hayward, Calif., model N-100, with a filtering time constant of approximately 7 s). A noninvasive blood pressure cuff was used to measure arterial blood pressure every 3 min. Fetal heart rate (FHR) was displayed continuously. Uterine activity was monitored with an external tocodynamometer or an internal uterine pressure catheter. Each patient received an intravenous infusion of 700–1000 mL of crystalloid solution through a peripheral catheter inserted into a vein in the dorsum of the hand. A lumbar epidural catheter was then inserted and taped in place.

An observer (either an attending anesthesiologist or a resident with >6 mo in the anesthesiology program) who was unaware of the study treatment established a baseline MHR. This was defined as a stable rate with no variability for four to five consecutive beats in the absence of uterine contractions.

The patients were then sequentially assigned to one of the following four groups: NS, EPI-5, EPI-10, or EPI-15. Fifteen patients received 3 mL of normal saline solution intravenously (NS group); other subjects were given an intravenous injection of 1.5% lidocaine with epinephrine 1:200,000. Specifically, 15 patients in the EPI-5 group received 1 mL; 14 patients in the EPI-10 group received 2 mL; and 15 patients in the EPI-15 group received 3 mL of the test solution. The EPI-5 and EPI-10 test doses were diluted to 3 mL with normal saline solution. All injections were given in the absence of uterine contractions and *immediately* after the establishment of baseline MHR. Parturients who developed uterine contraction within 1 min after the intravenous injection were also included in the study. An observer who was unaware of the study treatment then recorded the peak MHR, which was defined as the most rapid heart rate noted on the pulse oximeter within 1 min after the intravenous injection. The observer also questioned patients about the presence of tinnitus, dizziness, metallic taste, and palpitations and recorded their answers as well as his own opinion as to whether patients had received the test or the saline solution. No specific guidelines were given to the observer to discriminate among the groups, and the observer was not aware that different test doses were used. An obstetric nurse (blinded) and the authors (not blinded) observed the FHR tracing for signs of fetal distress.

We used the Newman-Keuls test to compare the four peak MHRs and estimated the lower bound of the 95% confidence interval from the EPI-15 group (peak MHR) to discriminate among the groups. We then calculated the sensitivity and specificity of the increase in MHR (baseline-to-peak criterion) in the four groups. The areas under the receiving operating characteristic (ROC) curves for each study group assessed overall performance of this test (range 0.5–1.0). A ROC curve plots 1 − specificity on the horizontal axis against the sensitivity on the vertical axis at various possible cutoff points. Thus, in effect, a ROC curve displays the trade-offs between sensitivity and specificity that a diagnostic test allows. The ROC curves and the area under the ROC curves were determined with LABROC 1, a program for IBM-PC-compatible microcomputers based on maximal likelihood estimation of a binormal ROC curve. LABROC 1 uses a set of continuously distributed data. The positive predictive value (+PV) determined the diagnostic accuracy in the presence of a positive test (increase in MHR). The negative predictive value (−PV) determined the diagnostic accuracy in the presence of a negative test (no increase in MHR). Sensitivity and specificity of the observer's clinical evaluation were also calculated, along with +PV and −PV. Finally, evaluation of the four symptoms as markers of intravascular injection of ETD was assessed by calculating specificity and sensitivity.

Table 1. Peak Maternal Heart Rate Increases in the Four Study Groups

Study group	Peak MHR (beats/min above baseline)	SD
NS (n = 15)	8	±10
EPI-5 (n = 15)	21	±8
EPI-10 (n = 14)	31.5	±13
EPI-15 (n = 15)	29	±9

MHR, maternal heart rate; NS, normal saline solution (3 mL IV); EPI-5 (1 mL IV), EPI-10 (2 mL IV), EPI-15 (3 mL IV), 1.5% lidocaine with epinephrine 1:200,000.

Data are means ± SD; Newman-Keuls test: NS < EPI-5 < EPI-10 = EPI-15 ($P < 0.05$).

Results

The results of the analysis of the peak MHR are shown in Table 1. The Newman-Keuls comparison test of the four peak MHRs showed NS < EPI-5 < EPI-10 = EPI-15 ($P < 0.05$). In the EPI-15 group, the average increase of the peak MHR was 29 ± 9 beats/min (mean ± SD) above the baseline. Using the lower bound of the 95% confidence interval for the EPI-15 group, we accepted an increase >10 beats/min above the baseline as diagnostic of intravascular injection of ETD. We then calculated sensitivity and specificity of the peak MHR in the four groups.

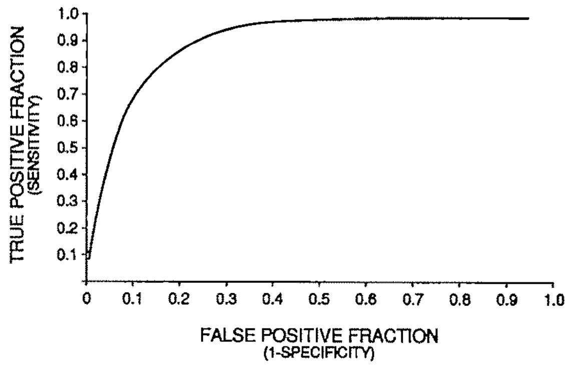

Figure 1. ROC curve and area under the curve assessing the level of diagnostic accuracy in distinguishing 15 patients in the NS group from 14 patients in the EPI-10 group. Area = 0.9289; SEM = 0.0554.

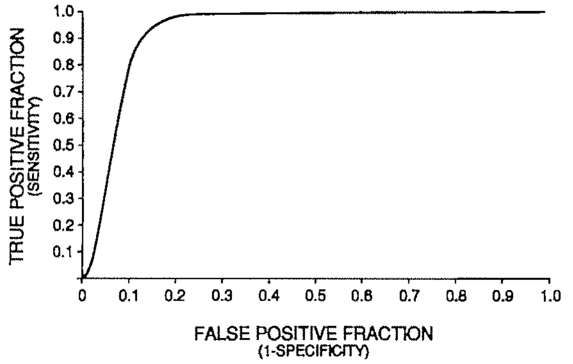

Figure 2. ROC curve and area under the curve assessing the level of diagnostic accuracy in distinguishing 15 patients in the NS group from 15 patients in the EPI-15 group. Area = 0.9107; SEM = 0.0539.

Table 2. Sensitivity and Specificity of the Peak Maternal Heart Rate and of the Observer Evaluation in the Four Study Groups

Study group	Peak MHR	Observer evaluation
Sensitivity		
EPI-5	87% (13/15 TP)	67% (10/15 TP)
EPI-10	100% (14/14 TP)	100% (14/14 TP)
EPI-15	100% (15/15 TP)	100% (15/15 TP)
Specificity		
NS	73% (11/15 TN)	93% (14/15 TN)

MHR, maternal heart rate; NS, normal saline solution (3 mL IV, *n* = 15); EPI-5 (1 mL IV, *n* = 15), EPI-10 (2 mL IV, *n* = 14), EPI-15 (3 mL IV, *n* = 15), 1.5% lidocaine with epinephrine 1:200,000; Sensitivity, number of true positives divided by the number of true positives plus false-negatives; Specificity, number of true negatives divided by the number of true negatives plus false-positives; TP, true positive; TN, true negative.

Table 3. Sensitivity and Specificity of the Four Symptoms Attributable to the Systemic Effects of the Test Dose

	Symptom			
Study group	Metallic taste	Dizziness	Palpitations	Tinnitus
Sensitivity				
EPI-5	1/15	4/15	4/15	0/15
EPI-10	3/14	6/14	3/14	0/14
EPI-15[a]	2/15	5/15	7/15	4/15
Specificity				
NS	13/15	13/15	14/15	15/15

NS, normal saline solution (3 mL IV, *n* = 15); EPI-5 (1 mL IV, *n* = 15), EPI-10 (2 mL IV, *n* = 14), EPI-15 (3 mL IV, *n* = 15), 1.5% lidocaine with epinephrine 1:200,000.

Sensitivity, number of true positives divided by the number of true positives plus false-negatives; Specificity, number of true negatives divided by the number of true negatives plus false-positives.

Sensitivity of the symptoms analyzed in combination reached 67% in the EPI-15 group.

The baseline-to-peak criterion identified all the intravascular injections in the EPI-15 group by design (the lower bound of the 95% confidence interval was calculated from the EPI-15 group) and in the EPI-10 group with a sensitivity of 100% and a −PV of 100%. Specificity of this test was 73% (11 of 15 true negatives), and the +PV ranged between 24% and 41%, assuming a prevalence of unintentional intravenous cannulation between 8% and 16%. The areas under the ROC curves for the EPI-10 and EPI-15 groups are displayed, respectively, in Figures 1 and 2. They were 0.83 for the EPI-5 group, 0.91 for the EPI-10 group, and 0.93 for the EPI-15 group.

The observers were also able to identify all the intravascular injections of ETD in the EPI-15 and EPI-10 groups with a sensitivity of 100%. Based on clinical evaluation, specificity reached 93% (14 of 15 true negatives). Results are shown in Table 2. The +PV was 55%–73% (prevalence 8%–16%), and the −PV 100%.

Sensitivity and specificity of the four symptoms, attributable to the systemic effects of an intravascular injection of ETD, were also calculated and did not reach clinical significance. The results are shown in Table 3.

The FHR monitor did not show any tracings indicative of fetal distress, and no medical intervention of any kind was ever required during the performance of the study. Noninvasive arterial blood pressure measurements provided frequently spurious results (movement artifacts), and the data were not used in the study.

Discussion

The intravenous injection of toxic doses of local anesthetics may cause seizures, cardiac arrest, and death (4). To prevent this occurrence during the performance of an epidural block, the concept of an "epidural test dose" (ETD) was developed.

An ETD should reliably provide an indication of unintentional intravenous insertion of an epidural catheter. The frequency of this mishap has been reported to be in the range of 3%–5% in the general population (5) and between 8% and 16% in pregnant patients (6), probably due to dilated epidural vessels (7).

Several techniques and agents have been proposed for use as ETDs. Since Moore and Batra (1) demonstrated a predictable heart rate increase after an intravenous injection of epinephrine (15 μg) in nonpregnant volunteers, the use of this agent as a marker for intravascular injection has become common. Recently, it was shown that the same heart rate changes could be induced with intravenous epinephrine (10 but not 5 μg) in nonpregnant volunteers (2).

In laboring patients, the sensitivity and specificity of epinephrine as a marker for intravascular injection are low (3) because of the wide variability in MHR. Isoproterenol has been suggested to replace epinephrine (8) as a component of an ETD in obstetrics; however, healthy and preeclamptic parturients have different chronotropic responses to the drug (9). The sensitivity of ephedrine is poor (<72%) (10). Finally, microbubbles of air have been found to be a reliable marker; however, the technique requires the use of a Doppler monitor over the precordium, and its placement must be "adequately confirmed and rechecked after changes in patient position" (11).

Our study shows that epinephrine is a sensitive marker of intravascular injection in laboring patients. Although analysis of the ROC curves (0.91–0.93) indicates acceptable overall performance of this test, a −PV of 100% provides strong evidence of its safety (absence of false-negative results). This conclusion is supported by the sensitivity of the baseline-to-peak criterion within 1 min and confirmed by the ability of the observer, who was unaware of the study treatment, to recognize all of the intravenous injections of either 10 or 15 μg of epinephrine.

The 1-min observation time was chosen because maximal changes in heart rate due to the injection of intravenous epinephrine occur within 30–45 s (1). Even though the venous return time from the epidural veins to the heart has never been compared with the venous return from the hand, 1 min closely approaches one circulation time in many parturients. In addition, limiting the MHR observation time to 1 min after the intravenous injection reduces the possible number of pain-induced MHR variations due to uterine contractions, and this in turn may improve the sensitivity and specificity of this technique. The importance of limiting the observation time to 1 min is also supported by the findings of Leighton et al. (3) who administered epinephrine (15 μg IV) to laboring parturients and noted a statistically significant increase in MHR at 45 s after the injection but not at 60 or 90 s. Indeed, other studies (12) in which MHR variations were observed for longer periods of time do not support the use of MHR accelerations as an indicator of intravascular injection in laboring parturients. Cartwright et al. (13) reduced the MHR observation time to 1 min after the epidural injection of ETD and showed that 24% of laboring parturients still had an MHR acceleration within that 1 min; however, in their study the criteria for defining the baseline MHR were not specified, and the time chosen to establish a baseline MHR ("during a period of uterine quiescence while the woman was lying comfortably") did not correlate temporally with the actual placement of the epidural catheter. A higher baseline MHR may be expected under those circumstances. In our study, to test our technique under clinical conditions we decided not to exclude those parturients who did experience uterine contractions within 1 min after the intravenous injection of ETD.

The components of an ETD should be safe for the baby as well as for the mother. Intravenous epinephrine causes a dose-dependent temporary reduction in uterine blood flow in animals (14) and may compromise fetal well-being in humans. In gravid ewes, 10 μg of intravenous epinephrine reduces uterine blood flow by 30%, and 20 μg causes an almost 50% decrease with no changes in FHR pattern (14). These reductions in uterine blood flow compare favorably with the 100% decrease noted in humans when intrauterine pressures reach 30–40 mm Hg (normal uterine contraction) (15). By monitoring the FHR we did not detect any signs of fetal distress in our patients after the injection of intravenous epinephrine, and this is in agreement with animal (14) and human studies (16). The safety of epinephrine in patients with a compromised uteroplacental reserve, as in preeclampsia, has yet to be determined.

Epidural test doses may also unintentionally be administered intrathecally; therefore drugs used as ETDs must be safe when injected into this compartment. Lidocaine (100 mg) (17) and chloroprocaine (100 mg) (18) are sensitive markers of intravenous injection and induce unmistakable symptoms in healthy male volunteers. However, if injected intrathecally in parturients, lidocaine may result in an undesirably high level of subarachnoid block and chloroprocaine carries the potential risk (19) of neurotoxicity. A smaller dose of lidocaine (45 mg) is not an accurate marker of intravascular injection in laboring patients (20). The safety of intrathecal isoproterenol has not been determined.

Specificity is also an essential feature of an ETD. A low incidence of false-positive results will avoid the unnecessary repetition of the procedure (replacement of a correctly inserted epidural catheter). In this study, the baseline-to-peak criterion reached 73%

specificity (11 of 15 true negatives) with a +PV of 24%–41%, whereas the observer's evaluation was 93% specific (14 of 15 true negatives) with a +PV of 55%–73%, suggesting that a blinded observer can clinically differentiate between the pattern of epinephrine-induced MHR accelerations (true-positive) and the pattern of pain-induced MHR accelerations (false-positive). This is not surprising and is in agreement with the previously mentioned study of Leighton et al. (3) in which the blinded investigator correctly distinguished between patients given epinephrine and those receiving normal saline solution despite the low sensitivity (50%) and specificity (20%) of their baseline-to-peak criterion. The different patterns of MHR accelerations in laboring parturients (epinephrine induced vs pain induced) were graphically recorded by van Zundert et al. (16) with the use of a direct electrocardiographic mode of FHR monitor located over the mother's precordium. The pattern of epinephrine-induced tachycardia was also described by Moore and Batra (1) in their original study in male volunteers as a rapidly developing, short-lived increase in heart rate (approximately 30 beats/min above the baseline) that followed intravenous injection (20–40-s delay) and returned to preinjection values within 25–35 s. Our observer was always able to recognize epinephrine-induced tachycardia in the EPI-15 and EPI-10 groups. He was also able to identify tachycardia from other sources (>10 beats/min above the baseline) in the NS group 75% of the time (4 of 15 false-positive by the baseline-to-peak criterion vs 1 of 15 false-positive based on the observer's evaluation). In practical terms, a +PV of 55%–73% implies that a positive test may yield false-positive results 45%–27% of the time, leading to unnecessary replacement of the epidural catheter.

Finally, in our study 10 μg of epinephrine was as effective as 15 μg in detecting intravascular injection. The epinephrine-induced reduction in uterine blood flow in animals has been shown to be dose dependent (14); therefore the use of 10 μg in humans may be warranted.

In conclusion, in this study we found that (a) epinephrine is a sensitive marker of intravascular injection in laboring patients; (b) within 1 min after injection, the baseline-to-peak criterion was a reliable indicator of intravenous injection; (c) 10 μg of epinephrine is as effective as 15 μg; (d) symptoms attributable to the systemic effects of our ETD were neither sensitive nor specific; (e) the pattern of epinephrine-induced tachycardia could be clinically differentiated from tachycardia from other sources; and (f) on the basis of our observer's evaluation, between 27% and 45% of epidural catheters may be unnecessarily repositioned in the presence of a positive test.

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Headache After Spinal Anesthesia for Cesarean Section: A Comparison of the 27-Gauge Quincke and 24-Gauge Sprotte Needles

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A high incidence of postdural puncture headache (PDPH) occurs after spinal anesthesia for cesarean section. To examine this problem, a study was conducted with the recently developed 24-gauge Sprotte and 27-gauge Quincke needles in patients undergoing elective and emergency cesarean section (n = 298). The needle to be used was assigned in a random manner: group I, 27-gauge Quincke (n = 147); group II, 24-gauge Sprotte (n = 151). During the postoperative period, patients were visited daily and asked specifically about the presence and severity of headache. The overall incidence of PDPH was 2% (n = 6), five in the Quincke group (3.5%) and one in the Sprotte group (0.7%). There was no significant difference in the incidence of PDPH between the two groups. Five headaches were classified as mild, and only one was moderate to severe. All headaches resolved quickly with conservative management and without blood patch. The authors conclude that the choice between a 27-gauge Quincke and a 24-gauge Sprotte needle does not influence the incidence of PDPH after spinal anesthesia for cesarean section.

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Spinal anesthesia for cesarean section is a popular and effective technique. Advantages over epidural block include the absence of risk of systemic local anesthetic toxicity, simplicity of technique, and rapid onset of surgical anesthesia; however, there is an inevitable risk of postdural puncture headache (PDPH) after spinal anesthesia, and until recently, the incidence of this complication was high enough to limit its use for cesarean section. The introduction of smaller gauge needles and of different needle-tip designs has created renewed enthusiasm for this technique. The 24-gauge Sprotte needle is associated with a very low incidence of spinal headache (1), and the widely used Quincke needle is now available in 26-, 27-, 29-, and 30-gauge sizes. The goal of this study was to compare, in a randomized clinical trial, the incidence of PDPH in patients undergoing cesarean section who received spinal anesthesia with either a 24-gauge Sprotte or 27-gauge Quincke needle.

Methods

The study was approved by the Institutional Ethics Committees of both participating hospitals (Royal Victoria Hospital and Jewish General Hospital). Two hundred ninety-eight patients consenting to spinal anesthesia for elective and emergency cesarean section were studied and were warned about the possible development of PDPH. Age, height, weight, gravidity, and parity were recorded for each patient. Group I (n = 147) had spinal anesthesia administered with a 27-gauge Quincke needle (Becton-Dickinson, Rutherford, N.J.); in group II (n = 151), the 24-gauge Sprotte needle was used (Pajunk, Geisingen, Germany). Patients received 1–1.5 L of intravenous normal saline solution at room temperature before block unless surgery was extremely urgent. The spinal needle was inserted at the L2-3 or L3-4 interspace in the sitting or lateral decubitus position, depending on the anesthetist's preference. Blocks were performed by staff, fellows, and residents under supervision. The bevel of the Quincke needle was kept parallel to the long axis of the dural fibers. An introducer was used in all patients. Hyperbaric 0.75% bupivacaine with 8.25% dextrose was the sole local anesthetic agent in the first 100 patients and the anesthetist chose a dose with the aim of obtaining a T-4 sensory

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block (dose range 10.5–15 mg). Preservative-free morphine (0.2 mg) was added to the syringe containing bupivacaine in all subsequent patients. At the Royal Victoria Hospital only, a transdermal scopolamine patch (1.5 mg) was placed at the time of surgery for emesis prophylaxis. The following information was recorded for each patient: number of attempts at puncture, position during block, bupivacaine dose, cephalad level of anesthesia obtained, occurrence of paresthesias, total amount of intravenous fluid administered, intraoperative analgesic supplement requirement, and the amount of ephedrine administered. Patients were seen daily by an anesthetist at the Royal Victoria Hospital and by a trained nurse at the Jewish General Hospital until discharge and were directly questioned at each visit about the presence of back pain and headache. A headache that was worse when sitting and relieved in the supine position was considered to be a PDPH and was classified according to severity: class I, mild headache when sitting or ambulating; class II, moderate to severe headache when sitting or ambulating; class III, moderate to severe headache when supine.

On each day that a PDPH was reported, patients were asked to score it on a standard 100-mm visual analogue scale. They were initially offered conservative management consisting of horizontal bed rest, oral analgesics, and oral caffeine. Blood patch therapy was explained at this time. Comparison of the following variables between the two groups was made with χ^2 analysis with Yates' correction factor when appropriate: incidence of elective and emergency surgery, PDPH, failure to obtain surgical anesthesia, need for intravenous analgesic supplement, paresthesias, shivering, back pain, and use of neuraxial morphine and transdermal scopolamine. A P value <0.05 was considered significant. A two-tailed t-test was used to compare age, height, weight, gravidity, parity, bupivacaine dose, number of days of follow-up, number of attempts to puncture the dura, ephedrine dose, and total volume of intravenous fluid administered. A P value <0.05 was considered significant.

Table 1. Patient Characteristics in the Two Study Groups

	27-Gauge Quincke needle (n = 147)	24-Gauge Sprotte needle (n = 151)
Age (yr)	30.3 ± 5.0	30.5 ± 4.5
Height (cm)	160.8 ± 6.1	161.9 ± 6.5
Weight (kg)	73.7 ± 10.7	75.1 ± 12.9
Gravidity	2.3 ± 1.3	2.4 ± 1.5
Parity	1.0 ± 1.1	1.0 ± 0.9

Mean ± SD.

Table 2. Nonparametric Clinical Variables in the Two Study Groups

	27-Gauge Quincke needle (n = 147)	24-Gauge Sprotte needle (n = 151)
Elective cases	93 (63)	96 (64)
Emergencies	54 (37)	55 (36)
PDPHs	5 (3.5)	1 (<1)
Failures	1 (<1)	0 (0)
Received IV analgesia	23 (16)	19 (13)
Paresthesia at spinal needle insertion	9 (6)	9 (6)
Intraoperative shivering	35 (24)	42 (28)
Postoperative back pain	67 (46)	57 (38)
Intrathecal morphine administered	94 (64)	95 (63)
Transdermal scopolamine patch placed	43 (29)	47 (31)

PDPH, postdural puncture headache; IV, intravenous.
Number of patients (percent).

Table 3. Parametric Clinical Variables in the Two Study Groups

	27-Gauge Quincke needle (n = 147)	24-Gauge Sprotte needle (n = 151)
Bupivacaine dose (mg)	13.6 (1.3)	13.8 (1.2)
Days follow-up	4.6 (0.8)	4.5 (0.8)
Number of attempts at LP	1.7 (1.1)	1.6 (1.0)
Ephedrine administered (mg)	10.6 (10.6)	12.4 (9.5)
Intraoperative IV fluids (mL)	2860 (539)	2889 (552)

LP, lumbar puncture; IV, intravenous.
Mean (± SD).

Results

Demographic data are shown in Table 1 and do not differ significantly between the two groups. Table 2 shows the incidence of elective and emergency surgery, PDPH, failure to obtain surgical anesthesia, need for intravenous analgesic supplement, paresthesias, shivering, back pain, and the use of neuroaxial morphine and transdermal scopolamine. Table 3 compares bupivacaine dose, number of days of follow-up, number of attempts to puncture the dura, ephedrine dose, and total volume of intravenous fluid administered. The incidence of shivering at elective surgery was 20%. The overall incidence of PDPH was 2% (n = 6), one PDPH occurring in the Sprotte group (0.7%) and five in the Quincke group (3.4%). This difference was not statistically significant.

Five of these headaches were classified as mild, and only one was moderate to severe. All recovered quickly with conservative management and without blood patch. Thirty episodes of headache that occurred in the postpartum period did not have the features of PDPH (10% incidence). Thirteen were in the Sprotte group and 17 in the Quincke group. This difference was not significant.

Discussion

Postdural puncture headache after cesarean section remains an important cause of postoperative morbidity. Of note, Chadwick et al. (2), in a review of closed claims in the ASA database, revealed that headaches are the third most frequent reason for claims against anesthesiologists in obstetrics (2). Median payment was $5000 (range $1000–$20,000).

It is accepted that the incidence of PDPH is directly related to needle size (3), but until recently the smallest size of Quincke needle available was 25 gauge. When used for cesarean section, the 25-gauge Quincke needle is associated with a high incidence of PDPH (e.g., 14.5% in a study by Cesarini et al. [1]). This has deterred many from freely adopting spinal anesthesia in obstetrics. The introduction of finer gauge Quincke needles (26-, 27-, 29-, and 30-gauge) has encouraged their evaluation for cesarean section. Puncture with both 29- and 30-gauge Quincke needles is usually performed through another needle placed in the epidural space, and this introduces the possibility of a dural puncture with a larger gauge epidural needle. Although the incidence of associated PDPH is very low, technical difficulties with these very small needles are frequently reported (4). Further experience would no doubt improve results.

The 26-gauge Quincke needle has not been widely studied in obstetrics, but reported PDPH rates have varied considerably (e.g., Barker [5] 2%; Snyder et al. [6] 25%). The 27-gauge Quincke needle is easy to use through an introducer, and spinal fluid returns adequately. Little information is available on the use of this needle in obstetrics.

Focus on the design of the needle tip is not new. In 1923, Greene (7) modified a beveled needle by rounding the tip and further beveling the edge in an effort to reduce dural trauma and PDPH. Hart and Whitacre (8) in 1951 introduced a solid-tip pencil-point needle with a lateral eye, believing that this would spread rather than cut dural fibers, and reported a low incidence of associated PDPH. Now known as the Whitacre needle, it has been available in a 22-gauge size for many years and has its loyal advocates; however, randomized trials comparing it with the Quincke needle were not attempted until recently. Snyder et al. (6) reported a 4% incidence of PDPH after 22-gauge Whitacre needle use, compared with 25% after 26-gauge Quincke needle use. A 25-gauge Whitacre needle is newly available, but its ability to reduce the incidence of PDPH has yet to be fully evaluated. In Sweden, Haraldson (9) in 1951 independently reported on the use of a pencil-point needle designed by Sjövall of very similar appearance to the Whitacre needle.

Sprotte et al. (10) reported in 1987 on a 6-yr experience with 22- and 24-gauge needles of his own design. The tip is solid, ogival in shape, with a lateral eye that is longer than the Whitacre needle eye. The incidence of PDPH was very low (0.02%), but obstetric patients were not included. Cesarini et al. (1) studied the 25-gauge Quincke and 24-gauge Sprotte needles in a randomized trial for cesarean section. No headaches were reported in the Sprotte group, but 14.5% were reported in the Quincke group.

The present study aimed to reduce the number of variables that might affect the incidence of PDPH. The population was entirely obstetric, and the surgery and local anesthetic agent used were standardized. Direct questioning revealed a very low and acceptable incidence of PDPH. There was no significant difference in the incidence of PDPH between the two needle groups with this sample size, although a definite trend was observed in favor of the Sprotte needle. It is possible that a study with a much larger sample size (800–1000 subjects per group) would reveal a significant advantage for the Sprotte needle. It was hoped that an observer questioning the patients would be unaware of which needle had been used. Unfortunately, manpower logistics rendered this impossible, but because objective criteria were used to determine the presence and classification of PDPH, the results should not be biased. It is possible that some patients developed a headache after discharge from the hospital, because no telephone follow-up was done. From a practical standpoint, however, no patient required prolonged hospitalization because of PDPH. A subgroup of patients received transdermal scopolamine (n = 97), and this drug could possibly influence the incidence of headache, although there was no evidence of this. Johnson et al. (11) have suggested that intrathecal fentanyl might lower the incidence of PDPH if added to the local anesthetic at cesarean section. Carney et al. (12) were not able to show that intrathecal morphine diminished the incidence of PDPH after cesarean section. In the present study, headaches only occurred in those who received intrathecal morphine. Although a clear trend was noted, statistical significance was lacking.

The comparative cost of Sprotte and Quincke needles is an important consideration. When purchased in bulk, the cost to the Royal Victoria Hospital in May 1991 was $2.44 CAN for the 27-gauge Quincke needle and $10.00 CAN for the 24-gauge Sprotte needle. There is obviously a considerable cost benefit in using the 27-gauge Quincke needle for routine cases, possibly reserving the Sprotte needle for an anticipated difficult block. The 27-gauge Quincke needle is more flexible, and the backflow of spinal fluid is slower than with the 24-gauge Sprotte needle. Those taking part in the study became adept and comfortable with both needles, but if asked for a subjective judgment, most would prefer the Sprotte. Anesthetic failures have been reported by Crone and Vogel (13) with the Sprotte needle and are thought to be related to the long lateral eye, with injection of some of the local anesthetic into the epidural space. No failures were seen with the Sprotte needle in this series.

The incidence of shivering at elective cesarean section (20%) was much lower in this study than that reported by Workhoeven (14) under epidural anesthesia (64%) with intravenous fluid at room temperature. The impression that less shivering occurs under spinal than under epidural anesthesia deserves further investigation.

Postoperative back pain was present in a surprisingly high number of patients, although the majority of these appeared totally undisturbed by this complaint. Evaluation of the severity and duration of back pain after spinal anesthesia for cesarean section is warranted. Back pain is a common complaint after spinal anesthesia for other types of surgery and may deter a patient from accepting the same anesthetic in the future (15).

In conclusion, spinal anesthesia with either the 24-gauge Sprotte or the 27-gauge Quincke needle was associated with a high degree of satisfaction from patients, anesthetists, and obstetricians and a low (2%) incidence of PDPH.

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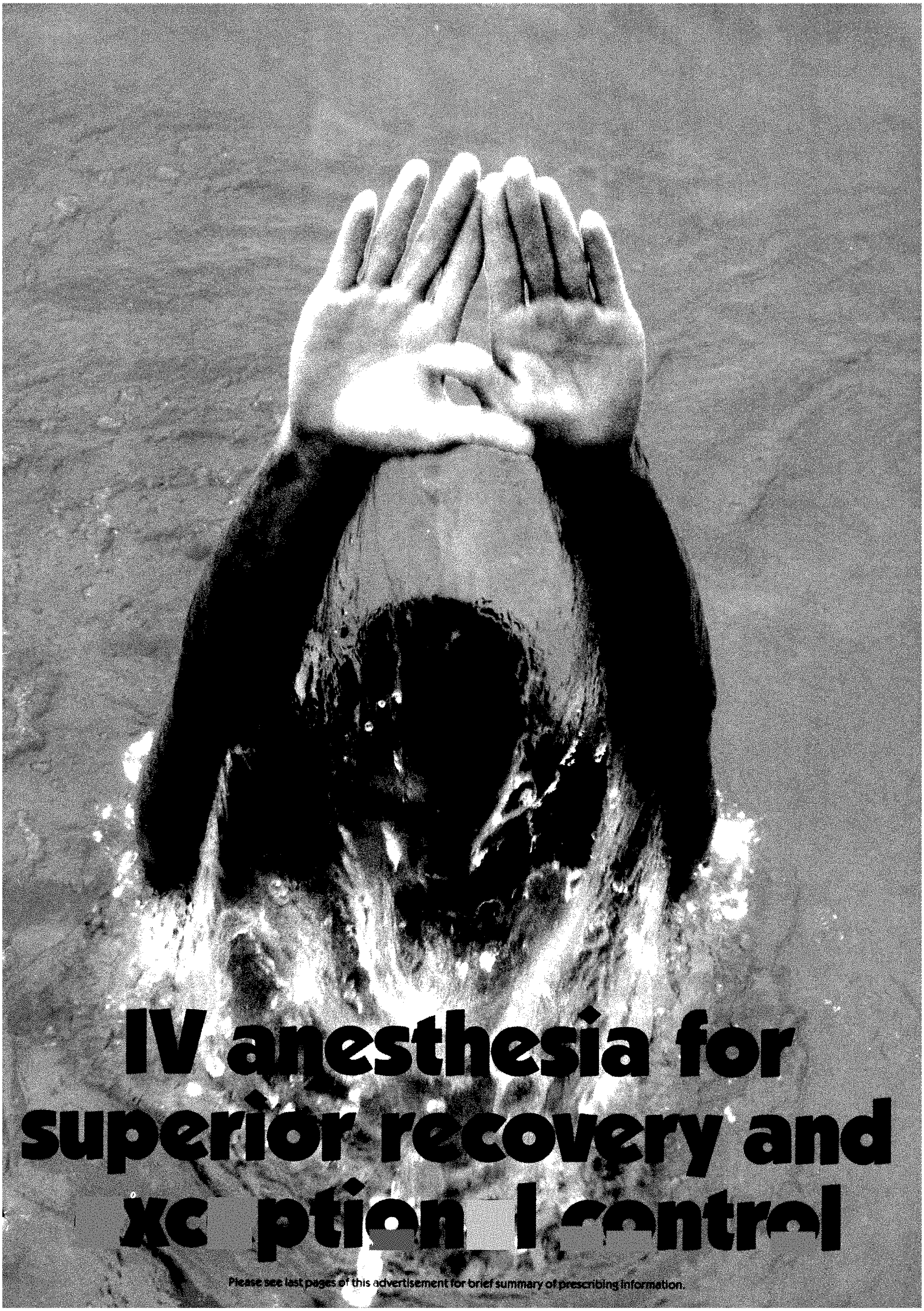

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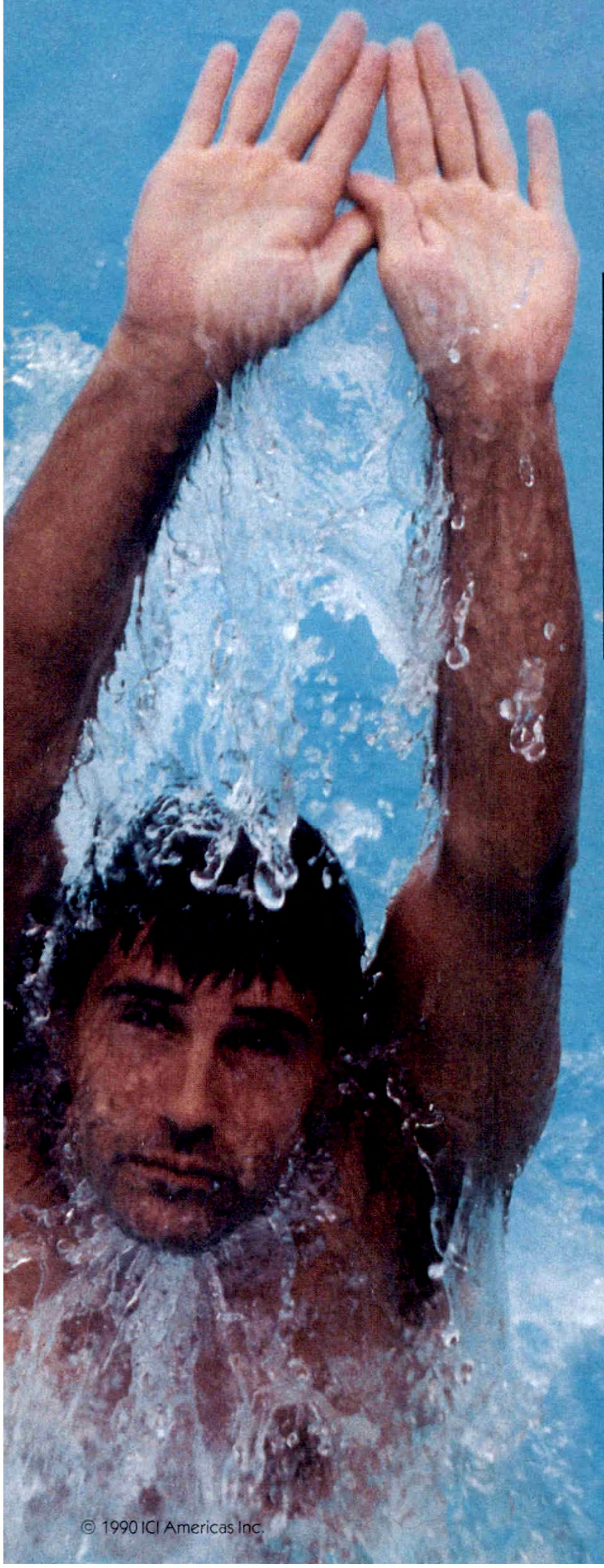
Superior
exceptional



Significantly improved speed and quality of recovery compared with thiopental/isoflurane

Mean postanesthesia recovery times (min)[1]

	DIPRIVAN	Thiopental/ isoflurane
Duration of anesthesia	**85***	**57**
Response to commands	3.5*	6.1
Fully oriented	5.5	9.4
Able to tolerate fluids	61*	130
"Ready" for discharge	138*	206

—adapted from Korttila et al, p A564[1]

*Statistically significant ($P < .05$).
Measurements taken from time of discontinuation of all maintenance anesthesia.

- Majority of patients are generally awake, responsive, and oriented within 8 minutes

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ecovery and anesthetic control

Significantly less nausea and vomiting than with thiopental/isoflurane

	DIPRIVAN	Thiopental/ isoflurane
Wetchler[2]	(n = 20)	(n = 20)
Nausea/vomiting	20%	65%
Sung et al[3]	(n = 49)	(n = 50)
Nausea/vomiting	8.1%	30%

As part of a balanced anesthetic technique, **DIPRIVAN is a cost-effective alternative to thiopental/isoflurane for induction and maintenance.**

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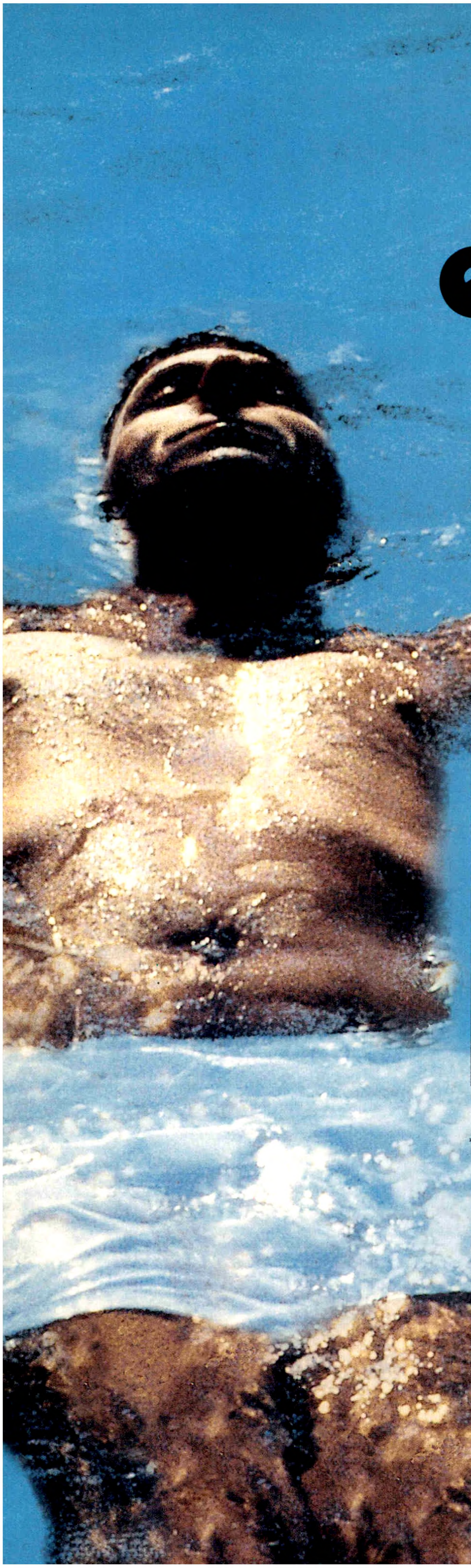
For induction and maintenance

DIPRIVAN®

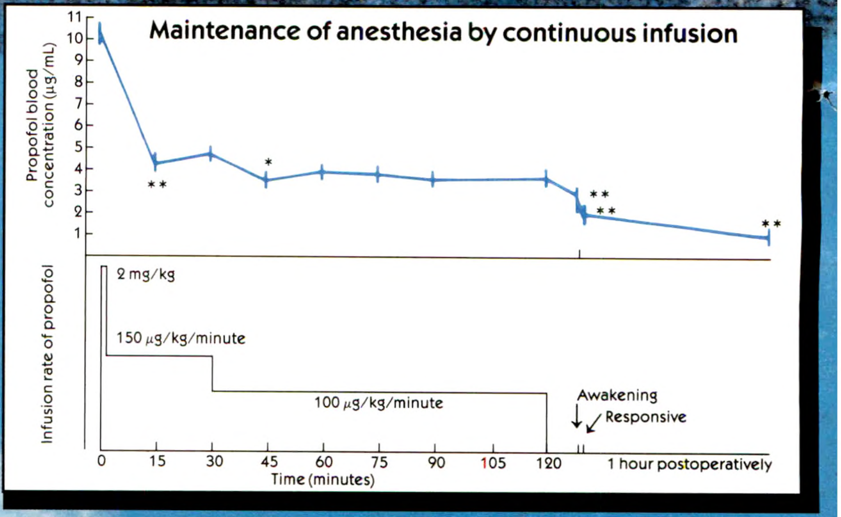
INJECTION propofol



Superior
exceptional

Maintenance of anesthesia as easily controlled as with isoflurane

- Steady state blood concentrations are proportional to rate of administration



—adapted from Herregods et al, p 364[4]

*Significant difference ($P < .05$) from previous value.
**$P < .02$. (Mean and SEM values are shown.)

After a loading dose of 2 mg/kg, anesthesia was maintained with 150 µg/kg/min for 30 minutes—then 100 µg/kg/min for 90 minutes.[4]

- Total body clearance exceeds estimates of hepatic blood flow[5]
- No active metabolites produced

As with most anesthetic agents, clearance rate of DIPRIVAN decreases in elderly patients.

ecovery and
nesthetic control

Hemodynamic effects are controllable and dose-dependent

- Blood pressure (BP) predictably decreases on induction (sometimes >30%) but is within acceptable ranges for healthy individuals*
- Hemodynamic effects during induction are generally more pronounced than with traditional IV induction agents

After initial decreases in BP following induction, hemodynamics return toward baseline

The cardiovascular effects of DIPRIVAN may be increased in patients who have received sedative or narcotic premedications.[†]

DIPRIVAN is not a narcotic agent
When used with N_2O/O_2 for maintenance, supplementation with IV analgesic agents is generally required; muscle relaxants may also be required.

Strict aseptic techniques must always be maintained while handling DIPRIVAN. DIPRIVAN is a single-use parenteral product and contains no antimicrobial preservatives. DIPRIVAN Injection should be prepared for use just prior to initiation of each individual anesthetic procedure. DIPRIVAN Injection should be drawn into sterile syringes immediately after ampules are opened. Administration should commence promptly and be completed within 6 hours after the ampules have been opened.

*Elderly, debilitated, and/or hypovolemic patients, and those rated ASA III/IV, may have more profound adverse cardiovascular responses.

[†] Induction dose requirements may be reduced.

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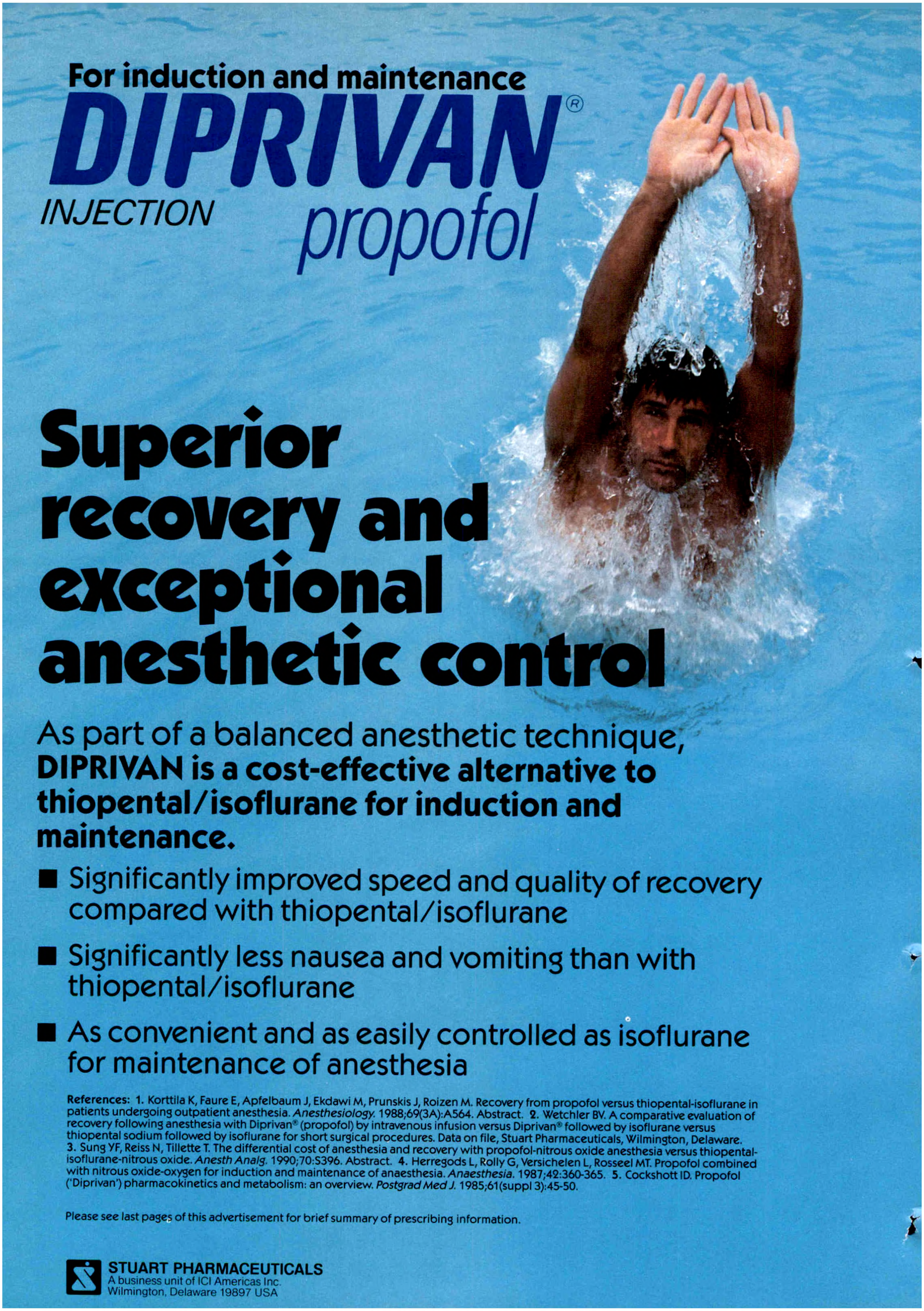
For induction and maintenance

DIPRIVAN®
INJECTION
propofol



For induction and maintenance

DIPRIVAN®

INJECTION propofol

Superior recovery and exceptional anesthetic control

As part of a balanced anesthetic technique, **DIPRIVAN is a cost-effective alternative to thiopental/isoflurane for induction and maintenance.**

- Significantly improved speed and quality of recovery compared with thiopental/isoflurane
- Significantly less nausea and vomiting than with thiopental/isoflurane
- As convenient and as easily controlled as isoflurane for maintenance of anesthesia

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STUART PHARMACEUTICALS
A business unit of ICI Americas Inc.
Wilmington, Delaware 19897 USA

DIPRIVAN® (propofol) Injection

EMULSION FOR IV ADMINISTRATION

(For full prescribing information, see package insert. A Brief Summary follows.)

CLINICAL PHARMACOLOGY—Individualization of Dosage: General: DIPRIVAN Injection is a potent sedative hypnotic agent which provides clinically useful anesthetic and sedative actions depending upon the dose and technique of administration. Important factors to consider include the types of preinduction and concomitant medications, age, ASA physical classification and level of debilitation of the patient, and ultimately, the dose and rate of administration of DIPRIVAN Injection. Individualization of dose and technique will provide a smooth induction and stable maintenance while reducing potential unwanted side effects. Patients with hypovolemia should have fluid-volume deficits corrected prior to administration of DIPRIVAN Injection. **Induction of Anesthesia:** Most adult patients under 55 years of age and classified ASA I or II require 2.0 to 2.5 mg/kg of DIPRIVAN Injection for induction when unpremedicated or when premedicated with oral benzodiazepines or intramuscular opioids. For induction, DIPRIVAN Injection should be titrated (approximately 40 mg every 10 seconds) against the response of the patient until the clinical signs show the onset of anesthesia. As with other sedative hypnotic agents, the amount of intravenous opioid and/or benzodiazepine premedication will influence the response of the patient to an induction dose of DIPRIVAN Injection. It is important to be familiar with and experienced with the intravenous use of DIPRIVAN Injection before treating elderly, debilitated and ASA III or IV patients. Due to the reduced clearance and higher blood levels, most elderly patients require approximately 1.0 to 1.5 mg/kg (approximately 20 mg every 10 seconds) of DIPRIVAN Injection for induction of anesthesia according to their condition and responses. A rapid bolus should not be used as this will increase the likelihood of undesirable cardiorespiratory depression including hypotension, apnea, airway obstruction and/or oxygen desaturation. (See DOSAGE AND ADMINISTRATION.) **Maintenance of Anesthesia:** Anesthesia can be maintained by administering DIPRIVAN Injection by infusion or intermittent IV bolus injection. The patient's clinical response will determine the infusion rate or the amount and frequency of incremental injections. When administering DIPRIVAN Injection by infusion, syringe pumps or volumetric pumps must be used to provide controlled infusion rates. **Continuous Infusion:** DIPRIVAN Injection 100 to 200 µg/kg/min administered in a variable rate infusion with 60%-70% nitrous oxide and oxygen provides anesthesia for patients undergoing general surgery. Maintenance by infusion of DIPRIVAN Injection should immediately follow the induction dose in order to provide satisfactory or continuous anesthesia during the induction phase. During this initial period following the induction dose higher rates of infusion are generally required (150 to 200 µg/kg/min) for the first 10 to 15 minutes. Infusion rates should subsequently be decreased 30%-50% during the first half-hour of maintenance. Changes in vital signs (increases in pulse rate, blood pressure, sweating and/or tearing) that indicate a response to surgical stimulation or lightening of anesthesia may be controlled by the administration of DIPRIVAN Injection 25 mg (2.5 mL) to 50 mg (5.0 mL) incremental boluses and/or by increasing the infusion rate. If vital sign changes are not controlled after a five minute period, other means such as an opioid, barbiturate, vasodilator or inhalation agent therapy should be initiated to control these responses. For minor surgical procedures (ie, body surface) 60%-70% nitrous oxide can be combined with a variable rate DIPRIVAN infusion to provide satisfactory anesthesia. With more stimulating surgical procedures (ie, intra-abdominal) supplementation with analgesic agents should be considered to provide a satisfactory anesthetic and recovery profile. When supplementation with nitrous oxide is not provided, administration rate(s) of DIPRIVAN Injection and/or opioids should be increased in order to provide adequate anesthesia. Infusion rates should always be titrated downward in the absence of clinical signs of light anesthesia until a mild response to surgical stimulation is obtained in order to avoid administration of DIPRIVAN Injection at rates higher than are clinically necessary. Generally, rates of 50 to 100 µg/kg/min should be achieved during maintenance in order to optimize recovery times. **Intermittent Bolus:** Increments of DIPRIVAN Injection 25 mg (2.5 mL) to 50 mg (5.0 mL) may be administered with nitrous oxide in patients undergoing general surgery. The incremental boluses should be administered when changes in vital signs indicate a response to surgical stimulation or light anesthesia. DIPRIVAN Injection has been used with a variety of agents commonly used in anesthesia such as atropine, scopolamine, glycopyrrolate, diazepam, depolarizing and nondepolarizing muscle relaxants, and opioid analgesics, as well as with inhalational and regional anesthetic agents. In the elderly, rapid bolus doses should not be used as this will increase cardiorespiratory effects including hypotension, apnea, airway obstruction and/or oxygen desaturation. Most elderly patients require a reduction of the recommended maintenance rates for healthy adults (< 55 years) to 50 to 100 µg/kg/min (3 to 6 mg/kg/h). **MAC SEDATION:** When DIPRIVAN Injection is administered for sedation, rates of administration should be individualized and titrated to clinical response. In most patients the rates of DIPRIVAN Injection administration will be approximately 25% of those used for maintenance of general anesthesia. During initiation of MAC sedation, slow infusion or slow injection techniques are preferable over rapid bolus administration. During maintenance of MAC sedation, a variable rate infusion is preferable over intermittent bolus dose administration. In the elderly, debilitated and ASA III or IV patients, rapid (single or repeated) bolus dose administration should not be used for MAC sedation. (See WARNINGS.) **A rapid bolus injection can result in undesirable cardiorespiratory depression including hypotension, apnea, airway obstruction and/or oxygen desaturation. Initiation of MAC Sedation:** For initiation of sedation, either an infusion or a slow injection method may be utilized while closely monitoring cardiorespiratory function. With the infusion method, sedation may be initiated by infusing DIPRIVAN Injection at 100 to 150 µg/kg/min (6 to 9 mg/kg/h) for a period of 3 to 5 minutes and titrating to the desired level of sedation while closely monitoring respiratory function. With the slow injection method for initiation, patients will require approximately 0.5 mg/kg administered over 3 to 5 minutes and titrated to clinical responses. When DIPRIVAN Injection is administered slowly over 3 to 5 minutes, most patients will be adequately sedated and the peak drug effect can be achieved while minimizing undesirable cardiorespiratory effects occurring at high plasma levels. In the elderly, debilitated, and ASA III or IV patients, rapid (single or repeated) bolus dose administration should not be used for MAC sedation. (See WARNINGS.) The rate of administration should be over 3-5 minutes and the dosage of DIPRIVAN Injection should be reduced to approximately 80% of the adult dosage in these patients according to their condition, responses, and changes in vital signs. (See DOSAGE AND ADMINISTRATION.) **Maintenance of MAC Sedation:** For maintenance of sedation, a variable rate infusion method is preferable over an intermittent bolus dose method. With the variable rate infusion method, patients will generally require maintenance rates of 25 to 75 µg/kg/min (1.5 to 4.5 mg/kg/h) during the first 10 to 15 minutes of sedation maintenance. Infusion rates should subsequently be decreased over time to 25 to 50 µg/kg/min and adjusted to clinical responses. In titrating to clinical effect, allow approximately 2 minutes for onset of peak drug effect. Infusion rates should always be titrated downward in the absence of clinical signs of light sedation until mild responses to stimulation are obtained in order to avoid sedative administration of DIPRIVAN Injection at rates higher than are clinically necessary. If the intermittent bolus dose method is used, increments of DIPRIVAN Injection 10 mg (1.0 mL) or 20 mg (2.0 mL) can be administered and titrated to desired level of sedation. With the intermittent bolus method of sedation maintenance there is the potential for respiratory depression, transient increases in sedation depth, and/or prolongation of recovery. In the elderly, debilitated, and ASA III or IV patients, rapid (single or repeated) bolus dose administration should not be used for MAC sedation. (See WARNINGS.) The rate of administration and the dosage of DIPRIVAN Injection should be reduced to approximately 80% of the adult dosage in these patients according to their condition, responses, and changes in vital signs. (See DOSAGE AND ADMINISTRATION.) DIPRIVAN Injection can be administered as the sole agent for maintenance of MAC sedation during surgical/diagnostic procedures. When DIPRIVAN sedation is supplemented with opioid and/or benzodiazepine medications, these agents increase the sedative and respiratory effects of DIPRIVAN and may also result in a slower recovery profile. (See PRECAUTIONS, Drug Interactions.) **INDICATIONS AND USAGE:** DIPRIVAN Injection is an IV anesthetic agent that can be used for both induction and/or maintenance of anesthesia as part of a balanced anesthetic technique for inpatient and outpatient surgery. DIPRIVAN Injection, when administered IV as directed, can be used to initiate and maintain monitored anesthesia care (MAC) sedation during diagnostic procedures. DIPRIVAN Injection may also be used for MAC sedation in conjunction with local/regional anesthesia in patients undergoing surgical procedures. (See PRECAUTIONS.) DIPRIVAN Injection is not recommended for use at this time in patients with increased intracranial pressure or impaired cerebral circulation, in obstetrics including cesarean section deliveries, in nursing mothers, and in pediatric patients. **CONTRAINDICATIONS:** DIPRIVAN Injection is contraindicated in patients with a known hypersensitivity to DIPRIVAN Injection or its components, or when general anesthesia or sedation are contraindicated. **WARNINGS:** For general anesthesia or monitored anesthesia care (MAC) sedation, **DIPRIVAN Injection should be administered only by persons trained in the administration of general anesthesia and not involved in the conduct of the surgical/diagnostic procedure. Patients should be continuously monitored and facilities for maintenance of a patent airway, artificial ventilation, and oxygen enrichment and circulatory resuscitation must be immediately available.** In the elderly, debilitated and ASA III or IV patients, rapid (single or repeated) bolus administration should not be used during general anesthesia or MAC sedation in order to minimize undesirable cardiorespiratory depression including hypotension, apnea, airway obstruction and/or oxygen desaturation. MAC sedation patients should be continuously monitored by persons not involved in the conduct of the surgical or diagnostic procedure; oxygen supplementation should be immediately available and provided where clinically indicated; and oxygen saturation should be monitored in all patients. Patients should be continuously monitored for early signs of hypotension, apnea, airway obstruction and/or oxygen desaturation. These cardiorespiratory effects are more likely to occur following rapid initiation (loading) boluses or during supplemental maintenance boluses, especially in the elderly, debilitated and ASA III or IV patients. DIPRIVAN Injection should not be coadministered through the same IV catheter with blood or plasma because compatibility has not been established. In vitro tests have shown that aggregates of the globular component of the emulsion vehicle have occurred with blood/plasma/serum from humans and animals. The clinical significance is not known. **Strict aseptic techniques must always be maintained during handling as DIPRIVAN Injection is a single-use parenteral product and contains no antimicrobial preservatives. The vehicle is capable of supporting rapid growth of microorganisms. (See DOSAGE AND ADMINISTRATION, Handling Procedures.) Failure to follow aseptic handling procedures may result in microbial contamination causing fever, infection/sepsis and/or other adverse consequences which could lead to life-threatening illness. PRECAUTIONS: General:** A lower induction dose and a slower maintenance rate of administration should be used in elderly, debilitated and ASA III or IV patients. (See CLINICAL PHARMACOLOGY—Individualization of Dosage.) Patients should be continuously monitored for early signs of significant hypotension and/or bradycardia. Treatment may include increasing the rate of intravenous fluid, elevation of lower extremities, use of pressor agents, or administration of atropine. Apnea often occurs during induction and may persist for more than 60 seconds. Ventilatory support may be required. Because DIPRIVAN Injection is an emulsion, caution should be exercised in patients with disorders of lipid metabolism such as primary hyperlipoproteinemia, diabetic hyperlipemia, and pancreatitis. The clinical criteria for discharge from the recovery/day surgery area established for each institution should be satisfied before discharge of the patient from the care of the anesthesiologist. When DIPRIVAN Injection is administered to an epileptic patient, there may be a risk of convulsion during the recovery phase. Transient local pain may occur during intravenous injection, which may be reduced by prior injection of IV lidocaine (1.0 mL of a 1% solution). Venous sequelae (phlebitis or thrombosis) have been reported rarely (< 1%). In two well-controlled clinical studies using dedicated intravenous catheters, no instances of venous sequelae were reported up to 14 days following induction. Pain can be minimized if the larger veins of the forearm or antecubital fossa are used. Accidental clinical extravasation and intentional injection into subcutaneous or perivascular tissues of animals caused minimal tissue reaction. Intra-arterial injection in animals did not induce local tissue effects. Accidental intra-arterial injection has been reported in patients, and other than pain, there were no major sequelae. Perioperative myoclonia, rarely including convulsions and opisthotonus, has occurred in a temporal relationship in cases in which DIPRIVAN Injection has been administered. Clinical features of anaphylaxis, which may include bronchospasm, erythema and hypotension, occur rarely following DIPRIVAN Injection administration, although use of other drugs in most instances makes the relationship to DIPRIVAN Injection unclear. There have been reports of pulmonary edema in temporal relationship to the administration of DIPRIVAN Injection, although a causal relationship is unknown. DIPRIVAN Injection has no vagolytic activity and has been associated with reports of bradycardia, occasionally profound, and/or asystole. The intravenous administration of anticholinergic agents (eg, atropine or glycopyrrolate) should be considered to modify potential increases in vagal tone due to concomitant agents (eg, succinylcholine) or surgical stimuli. There have been rare reports of cardiac arrest in temporal relationship to the administration of DIPRIVAN Injection. **Neurosurgical Anesthesia:** Studies to date indicate that DIPRIVAN Injection decreases cerebral blood flow, cerebral metabolic oxygen consumption, and intracranial pressure, and increases cerebrovascular resistance. DIPRIVAN Injection does not seem to affect cerebrovascular reactivity to changes in arterial carbon dioxide tension. Despite these findings, DIPRIVAN Injection is not recommended for use at this time in patients with increased intracranial pressure or impaired cerebral circulation because DIPRIVAN Injection may cause substantial decreases in mean arterial pressure, and consequently, substantial decreases in cerebral perfusion pressure. Further studies are needed to substantiate what happens to intracranial pressure following DIPRIVAN Injection when decreases in mean arterial and cerebral perfusion are prevented by appropriate measures. **Information for Patients:** Patients should be advised that performance of activities requiring mental alertness, such as operating a motor vehicle, or hazardous machinery or signing legal documents may be impaired for some time after general anesthesia or sedation. **Drug Interactions:** The induction dose requirements of DIPRIVAN Injection may be reduced in patients with intramuscular or intravenous premedication, particularly with narcotics (eg, morphine, meperidine, and fentanyl) and combinations of opioids and sedatives (eg, benzodiazepines, barbiturates, chloral hydrate, droperidol, etc.). These agents may increase the anesthetic or sedative effects of DIPRIVAN Injection and may also result in more pronounced decreases in systolic, diastolic, and mean arterial pressures and cardiac output. During maintenance of anesthesia or sedation, the rate of DIPRIVAN Injection administration should be adjusted according to the desired level of anesthesia or sedation and may be reduced in the presence of supplemental analgesic agents (eg, nitrous oxide or opioids). The concurrent administration of potent inhalational agents (eg, isoflurane, enflurane, and halothane) during maintenance with DIPRIVAN Injection has not been extensively evaluated. These inhalational agents can also be expected to increase the anesthetic or sedative and cardiorespiratory effects of DIPRIVAN Injection. DIPRIVAN Injection does not cause a clinically significant change in onset, intensity or duration of action of the commonly used neuromuscular blocking agents (eg, succinylcholine and nondepolarizing muscle relaxants). No significant adverse interactions with commonly used premedications or drugs used during anesthesia or sedation (including a range of muscle relaxants, inhalational agents, analgesic agents, and local anesthetic agents) have been observed. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Animal carcinogenicity studies have not been performed with propofol. In vitro and in vivo animal tests failed to show any potential for mutagenicity by propofol. Tests for mutagenicity included the Ames (using *Salmonella* sp) mutation test, gene mutation/gene conversion using *Saccharomyces cerevisiae*, in vitro cytogenetic studies in Chinese hamsters and a mouse micronucleus test. Studies in female rats at intravenous doses up to 15 mg/kg/day (6 times the maximum recommended human induction dose) for 2 weeks before pregnancy to day 7 of gestation did not show impaired fertility. Male fertility in rats was not affected in a dominant lethal study at intravenous doses up to 15 mg/kg/day for 5 days. **Pregnancy Category B:** Reproduction studies have been performed in rats and rabbits at intravenous doses of 15 mg/kg/day (6 times the recommended human induction dose) and have revealed no evidence of impaired fertility or harm to the fetus due to propofol. Propofol, however, has been shown to cause maternal deaths in rats and rabbits and decreased pup survival during the lactating period in dams treated with 15 mg/kg/day (or 6 times the recommended human induction dose). The pharmacological activity (anesthesia) of the drug on the mother is probably responsible for the adverse effects seen in the offspring. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human responses, this drug should be used during pregnancy only if clearly needed. **Labor and Delivery:** DIPRIVAN Injection is not recommended for obstetrics, including cesarean section deliveries. DIPRIVAN Injection crosses the placenta, and as with other general anesthetic agents, the administration of DIPRIVAN Injection may be associated with neonatal depression. **Nursing Mothers:** DIPRIVAN Injection is not recommended for use in nursing mothers because DIPRIVAN has been reported to be excreted in human milk and the effects of oral absorption of small amounts of propofol are not known. **Pediatric Use:** DIPRIVAN Injection is not recommended for use in pediatric patients because safety and effectiveness have not been established. **ADVERSE REACTIONS:** Adverse event information is derived from controlled clinical trials and worldwide marketing experience. In the description below, rates of the more common events represent US/Canadian clinical study results. Less frequent events are derived principally from publications and marketing experience in over 8 million patients; there are insufficient data to support an accurate estimate of their incidence rates. The adverse experience profile from reports of 150 patients in the US/Canadian MAC sedation clinical trials is similar to the profile established with DIPRIVAN Injection during anesthesia (see below). During MAC sedation clinical trials, significant respiratory events included cough, upper airway obstruction, apnea, hypoventilation, and dyspnea. The most common adverse events which occurred in more than 3% of the patients receiving DIPRIVAN Injection for MAC sedation included hypotension, nausea, headache, and injection site pain or hotness. The following estimates of adverse events for DIPRIVAN Injection are derived from reports of 2588 patients included in the US/Canadian studies. These studies were conducted using a variety of premedicants, varying lengths of surgical/diagnostic procedures and various other anesthetic/sedative agents. Most adverse events were mild and transient. The following adverse events were reported in patients treated with DIPRIVAN Injection. They are presented within each body system in order of decreasing frequency. **Incidence Greater than 1%—All events regardless of causality, derived from clinical trials. Body as a Whole:** Fever. **Cardiovascular:** Hypotension* (see also CLINICAL PHARMACOLOGY), Bradycardia, Hypertension, Arrhythmia. **Central Nervous System:** Movement*, Headache, Dizziness, Twitching. **Digestive:** Nausea** (15%), Vomiting*, Abdominal Cramping. **Injection Site:** Pain*, Burning/Stinging*. **Respiratory:** Hiccough, Cough (see also CLINICAL PHARMACOLOGY). **Skin and Appendages:** Rash. Incidence of unmarked events is 1%-3%; *3% to 9%; **10% or greater. **Incidence Less than 1%—Causal Relationship Probable, derived from clinical trials.** (Adverse events reported in the literature, not seen in clinical trials, are *italicized*.) **Body as a Whole:** Perinatal Disorder, Extremities Pain, Awareness, Chest Pain, Increased Drug Effect, Neck Rigidity/Stiffness, Trunk Pain. *Anaphylaxis/Anaphylactoid Reaction.* **Cardiovascular:** Tachycardia, Premature Ventricular Contractions, Syncope, Premature Atrial Contractions, Abnormal ECG, ST Segment Depression, Bundle Branch Block, Extrasystole, Myocardial Infarction, Heart Block, Atrioventricular Block, Second Degree A-V Block. **Central Nervous System:** Bucking/Jerking/Thrashing, Clonic/Myoclonic Movement, Hypertonia/Dystonia, Chills/Shivering, Somnolence, Tremor, Agitation, Confusion, Delirium, Paresthesia, Abnormal Dreams, Euphoria, Fatigue, Moaning, Rigidity, Combativeness, Depression. **Digestive:** Hypersalivation, Dry Mouth, Swallowing, Enlarged Parotid. **Injection Site:** Tingling/Numbness, Coldness, Discomfort, Phlebitis, Hives/Itching, Redness/Discoloration. **Metabolic/Nutritional:** Hyperlipemia. **Musculoskeletal:** Myalgia. **Respiratory:** Apnea (see also CLINICAL PHARMACOLOGY), Upper Airway Obstruction, Wheezing, Dyspnea, Hypoventilation, Bronchospasm, Burning in Throat, Sneezing, Tachypnea, Hyperventilation, Hypoxia, Pharyngitis. **Skin and Appendages:** Flushing, Urticaria, Pruritus. **Special Senses:** Amblyopia, Diplopia, Taste Perversion, Eye Pain, Tinnitus. **Urogenital:** Abnormal Urine, Urine Retention, *Green Urine*. **Incidence Less than 1%—Causal Relationship Unknown, derived from clinical trials.** (Adverse events reported in the literature, not seen in clinical trials, are *italicized*.) **Body as a Whole:** Asthenia. **Cardiovascular:** Atrial Fibrillation, Bigeminy, Hemorrhage, Edema, Ventricular Fibrillation, Supraventricular Tachycardia, *Myocardial Ischemia*. **Central Nervous System:** Emotional Lability, Anxiety, Hysteria, Insomnia, Generalized and Localized Seizures, *Opisthotonus, Hypotonia, Hallucinations, Neuropathy, Thinking Abnormal.* **Digestive:** Diarrhea. **Hematologic/Lymphatic:** Coagulation Disorder. **Metabolic/ Nutritional:** Hyperkalemia. **Respiratory:** Laryngospasm. **Skin and Appendages:** Diaphoresis, *Conjunctival Hyperemia*. **Special Senses:** Ear Pain, *Nystagmus*. **Urogenital:** Oliguria. In addition to those adverse events listed above, the following adverse event has been reported as a result of postmarketing experience: amorous behavior. **DOSAGE AND ADMINISTRATION:** Dosage and rate of administration should be individualized and titrated to the desired effect according to clinically relevant factors including preinduction and concomitant medications, age, ASA physical classification and level of debilitation of the patient. The following is abbreviated dosage and administration information which is only intended as a general guide in the use of DIPRIVAN Injection. Prior to administering DIPRIVAN Injection, it is imperative that the physician review and be completely familiar with the specific dosage and administration information detailed in the CLINICAL PHARMACOLOGY—Individualization of Dosage section. In the elderly, debilitated and ASA III or IV patients, rapid bolus doses should not be used in the methods of administration described below. (See WARNINGS.)**

Induction of Anesthesia	Dosage should be individualized and titrated. **Adults*:** Most patients require 2.0 to 2.5 mg/kg (approximately 40 mg every 10 seconds until induction onset). **Elderly, Debilitated and ASA III or IV Patients:** Most patients require 1.0 to 1.5 mg/kg (approximately 20 mg every 10 seconds until induction onset). For complete dosage information, see CLINICAL PHARMACOLOGY—Individualization of Dosage.
Maintenance of Anesthesia: Infusion	Variable rate infusion—titrated to the desired clinical effect. **Adults*:** Most patients require 100 to 200 µg/kg/min (6 to 12 mg/kg/h). **Elderly, Debilitated and ASA III or IV Patients:** Most patients require 50 to 100 µg/kg/min (3 to 6 mg/kg/h).
Maintenance of Anesthesia: Intermittent Bolus	Increments of 25 mg to 50 mg as needed. For complete dosage information, see CLINICAL PHARMACOLOGY—Individualization of Dosage.
Initiation of MAC Sedation	Dosage and rate should be individualized. **Adults*:** Slow infusion or slow injection techniques are preferable over rapid bolus administration. Most patients require an infusion of 100 to 150 µg/kg/min (6 to 9 mg/kg/h) or a slow injection of 0.5 mg/kg over 3 to 5 minutes. **Elderly, Debilitated and ASA III or IV Patients:** Most patients require dosages similar to adults, but must be given as a slow infusion or slow injection and not as a rapid bolus. (See WARNINGS.)
Maintenance of MAC Sedation	Dosage and rate should be titrated to clinical effect. **Adults*:** A variable rate infusion technique is preferable over an intermittent bolus technique. Most patients require an infusion of 25 to 75 µg/kg/min (1.5 to 4.5 mg/kg/h) or incremental bolus doses of 10 mg or 20 mg. **Elderly, Debilitated and ASA III or IV Patients:** Most patients require a 20% reduction of the adult dose. A rapid (single or repeated) bolus dose should not be used. (See WARNINGS.) For complete dosage information, see CLINICAL PHARMACOLOGY—Individualization of Dosage.

*Adults—healthy, less than 55 years of age

Handling Procedures: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. DIPRIVAN Injection must not be administered through filters with a pore size less than 5 µm because this could restrict the flow of DIPRIVAN and/or cause the breakdown of the emulsion. Do not use if there is evidence of separation of the phases of the emulsion. **Strict aseptic techniques must always be maintained during handling as DIPRIVAN Injection is a single-use parenteral product and contains no antimicrobial preservatives. The vehicle is capable of supporting rapid growth of microorganisms. Failure to follow aseptic handling procedures may result in microbial contamination causing fever, infection/sepsis and/or other adverse consequences which could lead to life-threatening illness.** DIPRIVAN Injection should be prepared for use just prior to initiation of each individual anesthetic/sedative procedure. The ampule neck surface or vial rubber stopper should be disinfected using 70% isopropyl alcohol. DIPRIVAN Injection should be drawn into sterile syringes immediately after ampules or vials are opened. When withdrawing DIPRIVAN Injection from vials, a sterile vent spike should be used. The syringe(s) should be labeled with appropriate information including the date and time the ampule or vial was opened. Administration should commence promptly and be completed within 6 hours after the ampules or vials have been opened. DIPRIVAN Injection should be prepared for single patient use only. Any unused portions of DIPRIVAN Injection, reservoirs, dedicated administration tubing and/or solutions containing DIPRIVAN Injection must be discarded at the end of the anesthetic procedure or at 6 hours, whichever occurs sooner. The IV line should be flushed every 6 hours and at the end of the anesthetic procedure to remove residual DIPRIVAN Injection.

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THE SYNERGY OF CO-INDUCTION

Optimal induction produces 1) unconsciousness and 2) a rapid progression to a state of anesthesia, with maintenance of stable cardiovascular functioning.[1]

However, even though high doses of hypnotics—such as thiopental or propofol—can achieve both endpoints, they can also cause significant hemodynamic changes. Therefore, it may be advantageous to manage hypnosis and anesthesia sequentially by employing a combination of function-specific agents.

Indeed, VERSED given in combination with a second agent can achieve hypnosis through the synergistic interaction of subanesthetic doses,[2-8] the goal being to maximize desired effects and reduce the undesired.

The advantage of co-induction

It is well established that induction agents potentiate each other when given in combination. One quarter of the hypnotic ED_{50} of VERSED can reduce the hypnotic ED_{50} of thiopental by as much as 75%.[3]

However, this degree of reduction occurs when thiopental is given one minute after VERSED, thereby achieving synchronous peak effects. The magnitude of interaction diminishes as the interval between the administration of the co-induction agents lengthens.

Dosing considerations with VERSED® (midazolam HCl/Roche) (IV)

When VERSED is used before other intravenous agents for induction of anesthesia, the initial dose of each agent may be significantly reduced, at times to as low as 25% of the usual initial dose of the individual agents.

As a standard precaution, prior to I.V. administration of VERSED in any dose, oxygen and resuscitative equipment should be immediately available. VERSED should be used as an induction agent only by persons trained in anesthesiology and who are familiar with all dosing and administration guidelines. Reduce dosage in elderly or debilitated patients, in patients receiving narcotic premedication and in those with limited pulmonary reserve.

It is recommended that patients do not drive or operate hazardous machinery after receiving VERSED until the effects of the drug (*e.g.*, drowsiness) are gone or until the day after anesthesia, whichever is longer. The decision must be individualized.

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IDEAS IN ANESTHESIA

AN ONGOING SERIES

Please see summary of product information on following page.

References: 1. Wilenkin RL. Management of general anesthesia. In: Miller RD, ed. *Anesthesia.* 3rd ed. New York: Churchill Livingstone; 1990:1335-1346. 2. Vinik HR, Bradley EL Jr, Kissin I. Midazolam for coinduction of thiopental anesthesia in patients. *Anesthesiology.* 1990;73(3A):A1216. 3. Tverskoy M, et al. Midazolam-thiopental anesthetic interaction in patients. *Anesth Analg.* 1988;67:342-345. 4. Tverskoy M, et al. Midazolam acts synergistically with methohexitone for induction of anaesthesia. *Br J Anaesth.* 1989;63:109-112. 5. Short TG, Galletly DC, Plummer JL. Hypnotic and anaesthetic action of thiopentone and midazolam alone and in combination. *Br J Anaesth.* 1991;66:13-19. 6. Kissin I, et al. Alfentanil potentiates midazolam-induced unconsciousness in subanalgesic doses. *Anesth Analg.* 1990;71:65-69. 7. Vinik HR, Bradley EL Jr, Kissin I. Midazolam-alfentanil synergism for anesthetic induction in patients. *Anesth Analg.* 1989;69:213-217. 8. Ben-Shlomo I, et al. Midazolam acts synergistically with fentanyl for induction of anaesthesia. *Br J Anaesth.* 1990;64:45-47.

VERSED®
midazolam HCl/Roche ℂ
INJECTION

Before prescribing, please consult complete product information, a summary of which follows:

> Intravenous VERSED has been associated with respiratory depression and respiratory arrest, especially when used for conscious sedation. In some cases, where this was not recognized promptly and treated effectively, death or hypoxic encephalopathy has resulted. Intravenous VERSED should be used only in hospital or ambulatory care settings, including physicians' offices, that provide for continuous monitoring of respiratory and cardiac function. Immediate availability of resuscitative drugs and equipment and personnel trained in their use should be assured. (See WARNINGS.)
>
> The initial intravenous dose for conscious sedation may be as little as 1 mg, but should not exceed 2.5 mg in a normal healthy adult. Lower doses are necessary for older (over 60 years) or debilitated patients and in patients receiving concomitant narcotics or other CNS depressants. The initial dose and all subsequent doses should never be given as a bolus; administer over at least 2 minutes and allow an additional 2 or more minutes to fully evaluate the sedative effect. The use of the 1 mg/mL formulation or dilution of the 1 mg/mL or 5 mg/mL formulation is recommended to facilitate slower injection. Consult complete product information under DOSAGE AND ADMINISTRATION for complete dosing information.

CONTRAINDICATIONS: Patients with known hypersensitivity to the drug.

Benzodiazepines are contraindicated in patients with acute narrow angle glaucoma; may be used in open angle glaucoma only if patients are receiving appropriate therapy.

Not intended for intrathecal or epidural administration due to the presence of the preservative benzyl alcohol.

WARNINGS: Never use without individualization of dosage. Prior to IV use in any dose, ensure immediate availability of oxygen, resuscitative equipment and skilled personnel for maintenance of a patent airway and support of ventilation. Continuously monitor for early signs of underventilation or apnea, which can lead to hypoxia/cardiac arrest unless effective countermeasures are taken immediately. Vital signs should continue to be monitored during the recovery period.

Because IV VERSED depresses respiration, and opioid agonists and other sedatives can add to this depression, it should be administered as an induction agent only by a person trained in general anesthesia and should be used for conscious sedation only in the presence of personnel skilled in early detection of underventilation, maintaining a patent airway and supporting ventilation. **For conscious sedation, do not administer IV by rapid or single bolus.** Serious cardiorespiratory adverse events have occurred. These have included respiratory depression, apnea, respiratory arrest and/or cardiac arrest, sometimes resulting in death. There have been rare reports of hypotensive episodes requiring treatment during or after diagnostic or surgical manipulations in patients who have received VERSED. Hypotension occurred more frequently in the conscious sedation studies in patients premedicated with narcotic.

Reactions such as agitation, involuntary movements, hyperactivity and combativeness have been reported. These may be due to inadequate or excessive dosing or improper administration; however, the possibility of cerebral hypoxia or true paradoxical reactions should be considered. Should these reactions occur, response to each dose of VERSED and all other drugs should be evaluated before proceeding.

Concomitant use of barbiturates, alcohol or other CNS depressants may increase the risk of underventilation or apnea and may contribute to profound and/or prolonged drug effect. Narcotic premedication also depresses the ventilatory response to carbon dioxide stimulation.

Higher risk surgical, elderly or debilitated patients require lower dosages for induction of anesthesia, premedicated or not. Patients with chronic obstructive pulmonary disease are unusually sensitive to the respiratory depressant effect of VERSED. Patients with chronic renal failure and patients with congestive heart failure eliminate midazolam more slowly. Because elderly patients frequently have inefficient function of one or more organ systems, and because dosage requirements have been shown to decrease with age, reduce initial dosage and consider possibility of a profound and/or prolonged effect.

Do not administer in shock, coma, acute alcohol intoxication with depression of vital signs. Particular care should be exercised in the use of IV VERSED in patients with uncompensated acute illnesses, such as severe fluid or electrolyte disturbances.

Guard against unintended intra-arterial injection; hazards in humans unknown. Avoid extravasation.

VERSED should only be administered IM or IV. Safety and efficacy of other routes of administration are not established.

Gross tests of recovery from the effects of VERSED cannot alone predict reaction time under stress. This drug is never used alone during anesthesia, and the contribution of other perioperative drugs and events can vary. The decision as to when patients may engage in activities requiring mental alertness must be individualized; it is recommended that no patient should operate hazardous machinery or a motor vehicle until the effects of the drug, such as drowsiness, have subsided or until the day after anesthesia, whichever is longer.

Usage in Pregnancy: An increased risk of congenital malformations associated with the use of benzodiazepines (diazepam and chlordiazepoxide) has been suggested in several studies. If VERSED is used during pregnancy, apprise the patient of the potential hazard to the fetus.

PRECAUTIONS: *General:* Decrease intravenous doses in elderly and debilitated patients. These patients will also probably take longer to recover completely after VERSED for induction of anesthesia.

VERSED does not protect against increased intracranial pressure or against the heart rate rise and/or blood pressure rise associated with endotracheal intubation under light general anesthesia.

Information for patients: Communicate the following information and instructions to the patient when appropriate: 1. Inform your physician about any alcohol consumption and medicine you are now taking, including nonprescription drugs. Alcohol has an increased effect when consumed with benzodiazepines; therefore, caution should be exercised regarding simultaneous ingestion of alcohol and benzodiazepines. 2. Inform your physician if you are pregnant or are planning to become pregnant. 3. Inform your physician if you are nursing.

Drug interactions: The sedative effect of IV VERSED is accentuated by premedication,

particularly narcotics (*e.g.*, morphine, meperidine, fentanyl) and also secobarbital and Innovar (fentanyl and droperidol). Consequently, adjust the dosage according to the type and amount of premedication.

A moderate reduction in induction dosage requirements of thiopental (about 15%) has been noted following use of IM VERSED for premedication.

IV administration of VERSED decreases the minimum alveolar concentration (MAC) of halothane required for general anesthesia. This decrease correlates with the dose of VERSED administered.

Although the possibility of minor interactive effects has not been fully studied, VERSED and pancuronium have been used together in patients without noting clinically significant changes in dosage, onset or duration. VERSED does not protect against the characteristic circulatory changes noted after administration of succinylcholine or pancuronium, or against the increased intracranial pressure noted following administration of succinylcholine. VERSED does not cause a clinically significant change in dosage, onset or duration of a single intubating dose of succinylcholine.

No significant adverse interactions with commonly used premedications or drugs used during anesthesia and surgery (including atropine, scopolamine, glycopyrrolate, diazepam, hydroxyzine, d-tubocurarine, succinylcholine and nondepolarizing muscle relaxants) or topical local anesthetics (including lidocaine, dyclonine HCl and Cetacaine) have been observed.

Clearance of midazolam and certain other benzodiazepines may be delayed with concomitant administration of cimetidine (but not ranitidine). Clinical significance of this interaction is unclear.

Drug/laboratory test interactions: Midazolam has not been shown to interfere with clinical laboratory test results.

Carcinogenesis, mutagenesis, impairment of fertility: Midazolam maleate was administered to mice and rats for two years. At the highest dose (80 mg/kg/day) female mice had a marked increase in incidence of hepatic tumors and male rats had a small but significant increase in benign thyroid follicular cell tumors. These tumors were found after chronic use, whereas human use will ordinarily be of single or several doses.

Midazolam did not have mutagenic activity in tests that were conducted.

A reproduction study in rats did not show any impairment of fertility at up to ten times the human IV dose.

Pregnancy: Teratogenic effects: Pregnancy Category D. See WARNINGS section.

Midazolam maleate injectable, at 5 and 10 times the human dose, did not show evidence of teratogenicity in rabbits and rats.

Labor and delivery: Use in obstetrics has not been evaluated. Because midazolam is transferred transplacentally and because other benzodiazepines given in the last weeks of pregnancy have resulted in neonatal CNS depression, VERSED is not recommended for obstetrical use.

Nursing mothers: Excreted in human milk. Not recommended for use in nursing mothers.

Pediatric use: Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS: See WARNINGS concerning serious cardiorespiratory events and possible paradoxical reactions. Fluctuations in vital signs following parenteral administration were the most frequently seen findings and included decreased tidal volume and/or respiratory rate decrease (23.3% of patients following IV and 10.8% of patients following IM administration) and apnea (15.4% of patients following IV administration), as well as variations in blood pressure and pulse rate.

Following IM injection: headache (1.3%); local effects at IM site: pain (3.7%), induration (0.5%), redness (0.5%), muscle stiffness (0.3%).

IM administration to elderly and/or high-risk surgical patients has been associated with rare reports of death under circumstances compatible with cardiorespiratory depression. In most of these cases, patients also received other CNS depressants capable of depressing respiration, especially narcotics.

Following IV administration: hiccoughs (3.9%), nausea (2.8%), vomiting (2.6%), coughing (1.3%), "oversedation" (1.6%), headache (1.5%), drowsiness (1.2%); local effects at the IV site: tenderness (5.6%), pain during injection (5.0%), redness (2.6%), induration (1.7%), phlebitis (0.4%). Other effects (<1%) mainly following IV administration: *Respiratory:* Laryngospasm, bronchospasm, dyspnea, hyperventilation, wheezing, shallow respirations, airway obstruction, tachypnea. *Cardiovascular:* Bigeminy, premature ventricular contractions, vasovagal episode, bradycardia, tachycardia, nodal rhythm. *Gastrointestinal:* Acid taste, excessive salivation, retching. *CNS/Neuromuscular:* Retrograde amnesia, euphoria, hallucination, confusion, argumentativeness, nervousness, anxiety, grogginess, restlessness, emergence delirium or agitation, prolonged emergence from anesthesia, dreaming during emergence, sleep disturbance, insomnia, nightmares, athetoid movements, seizure-like activity, ataxia, dizziness, dysphoria, slurred speech, dysphonia, paresthesia. *Special Sense:* Blurred vision, diplopia, nystagmus, pinpoint pupils, cyclic movements of eyelids, visual disturbance, difficulty focusing eyes, ears blocked, loss of balance, lightheadedness. *Integumentary:* Hive-like elevation at injection site, swelling or feeling of burning, warmth or coldness at injection site. *Hypersensitivity:* Allergic reactions, including anaphylactoid reactions, hives, rash, pruritus. *Miscellaneous:* Yawning, lethargy, chills, weakness, toothache, faint feeling, hematoma.

Drug Abuse and Dependence: Available data concerning the drug abuse and dependence potential of midazolam suggest that its abuse potential is at least equivalent to that of diazepam.

OVERDOSAGE: Manifestations would resemble those observed with other benzodiazepines (*e.g.*, sedation, somnolence, confusion, impaired coordination, diminished reflexes, coma, untoward effects on vital signs). No specific organ toxicity would be expected.

DOSAGE AND ADMINISTRATION: VERSED is a potent sedative agent which requires slow administration and individualization of dosage. Clinical experience has shown VERSED to be 3 to 4 times as potent per mg as diazepam. BECAUSE SERIOUS AND LIFE-THREATENING CARDIORESPIRATORY ADVERSE EVENTS HAVE BEEN REPORTED, PROVISION FOR MONITORING, DETECTION AND CORRECTION OF THESE REACTIONS MUST BE MADE FOR EVERY PATIENT TO WHOM VERSED INJECTION IS ADMINISTERED, REGARDLESS OF AGE OR HEALTH STATUS. Excess doses or rapid or single bolus intravenous administration may result in respiratory depression and/or arrest. (See WARNINGS.) Prior to use refer to the DOSAGE AND ADMINISTRATION section in the complete product information.

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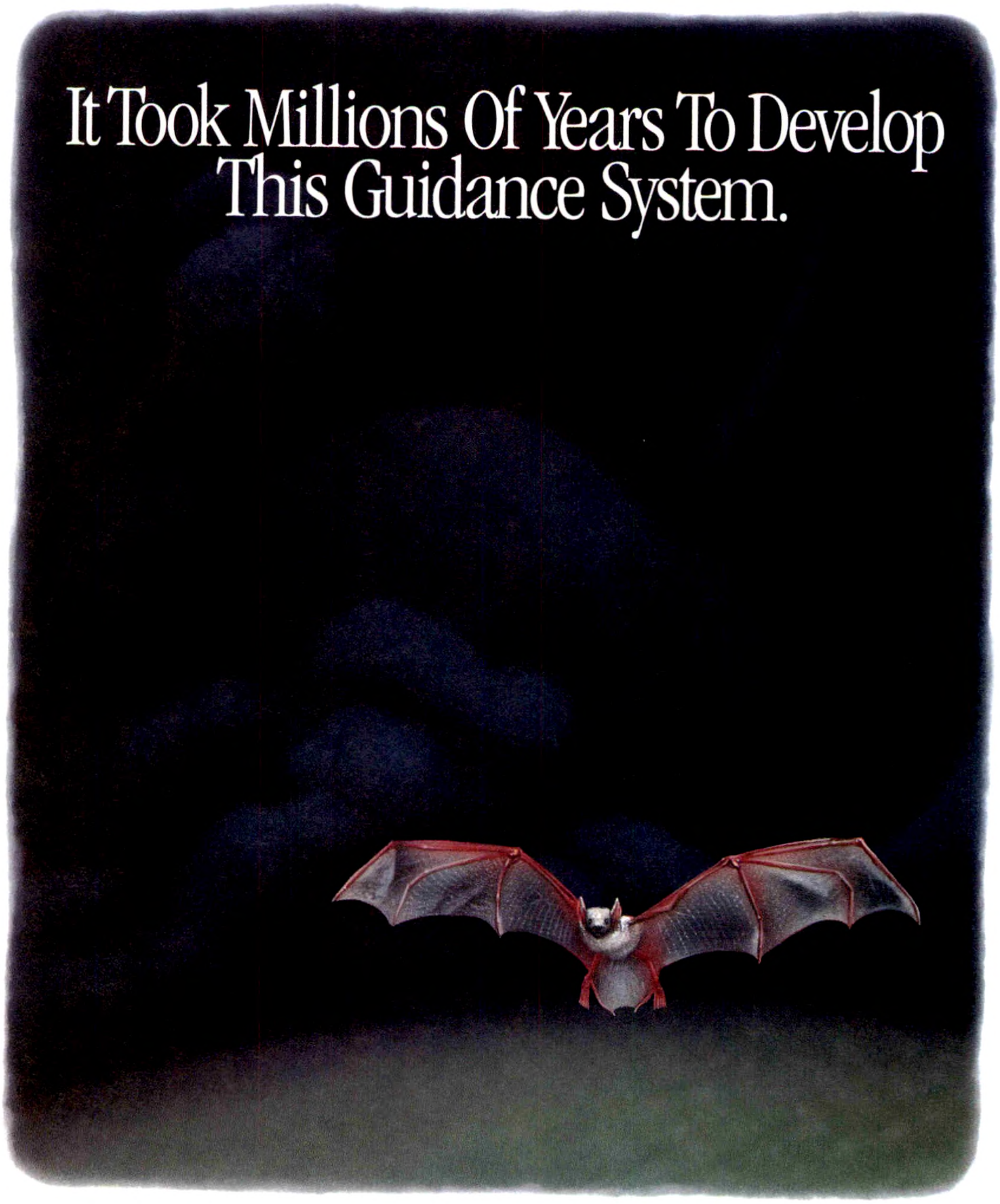
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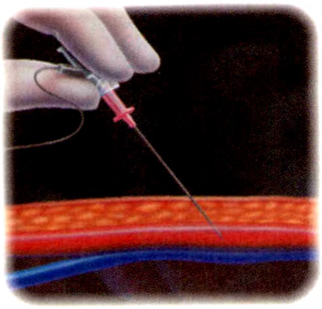

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SmartNeedle Vascular Access Guidance System designed in conjunction with Paul G. Yock, M.D. This product is intended for use by or under the direction of a physician. Prior to use, it is important to read the package insert thoroughly for instructions on use, warnings and potential complications associated with the use of this device. Manufactured under the following patent: United States, 4,887,606. Other U.S. and foreign patents pending. ©1992 Peripheral Systems Group

A specific reversal agent for benzodiazepine sedation

- MAZICON (flumazenil/Roche) rapidly and specifically reverses sedation produced by any benzodiazepine
- Promptly restores patients to consciousness—often within minutes of reaching an effective dose
- Reverses benzodiazepine sedative effects only—not the effects of narcotics or other CNS agents

Adverse effects

The most common side effects in clinical trials were nausea and vomiting (11%), dizziness (10%), agitation (3-9%) and injection-site pain (3-9%).

Wake Up Call for Benzodiazepine Sedation

Seizures

MAZICON is associated with seizures, most often in patients on benzodiazepines for long-term sedation or patients showing signs of serious cyclic antidepressant overdose. Practitioners should individualize the dosage and be prepared to manage seizures.

ROCHE

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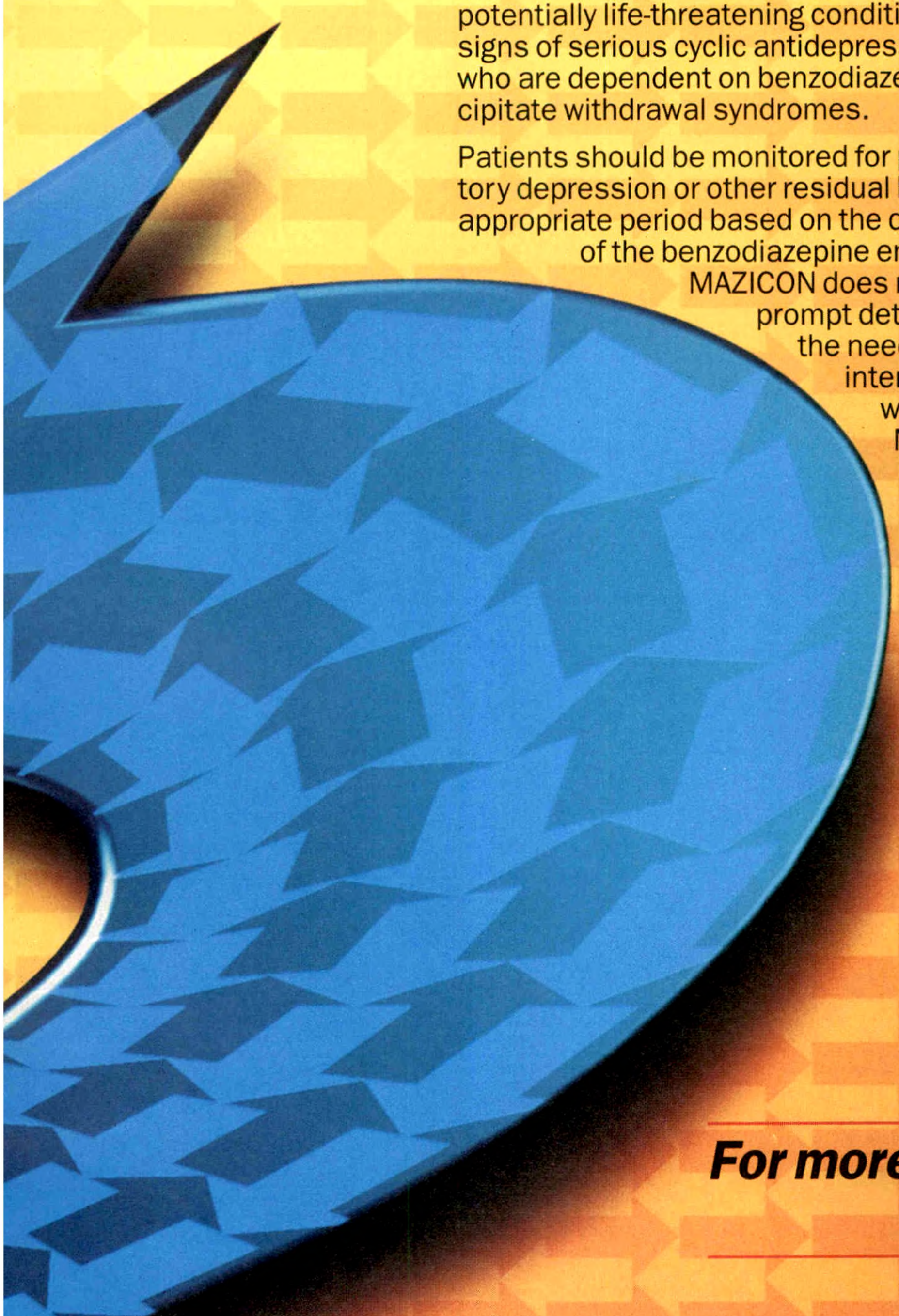


Important safety information

Contraindicated in hypersensitivity to benzodiazepines or MAZICON; in patients taking benzodiazepines for control of potentially life-threatening conditions; and in patients showing signs of serious cyclic antidepressant overdose. In patients who are dependent on benzodiazepines, MAZICON may precipitate withdrawal syndromes.

Patients should be monitored for possible resedation, respiratory depression or other residual benzodiazepine effects for an appropriate period based on the dose and duration of effect of the benzodiazepine employed. The availability of MAZICON does not diminish the need for prompt detection of hypoventilation and the need to be prepared to effectively intervene by establishing an airway and assisting ventilation. MAZICON has not been established as an effective treatment for benzodiazepine-induced hypoventilation.

For more information call:
1-800-756-7654

Available in 5-mL and 10-mL vials.

0.1 mg/mL
mazicon I.V.™
flumazenil/Roche

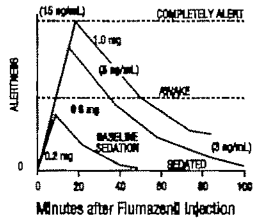
The reversal agent you've been waiting for

MAZICON™
(flumazenil/Roche)
INJECTION

DESCRIPTION: MAZICON™ (flumazenil/Roche) is a benzodiazepine receptor antagonist. Chemically, flumazenil is ethyl 8-fluoro-5,6-dihydro-5-methyl-6-oxo-4H-imidazo[1,5-a](1,4) benzodiazepine-3-carboxylate. Flumazenil has an imidazobenzodiazepine structure, a calculated molecular weight of 303.3.
Flumazenil is a white to off-white crystalline compound with an octanol:buffer partition coefficient of 14 to 1 at pH 7.4. It is insoluble in water but slightly soluble in acidic aqueous solutions. MAZICON is available as a sterile parenteral dosage form for intravenous administration. Each mL contains 0.1 mg of flumazenil compounded with 1.8 mg of methylparaben, 0.2 mg of propylparaben, 0.9% sodium chloride, 0.01% edetate disodium, and 0.01% acetic acid; the pH is adjusted to approximately 4 with hydrochloric acid and/or, if necessary, sodium hydroxide.

CLINICAL PHARMACOLOGY: Flumazenil, an imidazobenzodiazepine derivative, antagonizes the actions of benzodiazepines on the central nervous system. Flumazenil competitively inhibits the activity at the benzodiazepine recognition site on the GABA/benzodiazepine receptor complex. Flumazenil is a weak partial agonist in some animal models of activity, but has little or no agonist activity in man.
Flumazenil does not antagonize the central nervous system effects of drugs affecting GABA-ergic neurons by means other than the benzodiazepine receptor (including ethanol, barbiturates, or general anesthetics) and does not reverse the effects of opioids.
PHARMACODYNAMICS: Intravenous MAZICON has been shown to antagonize sedation, impairment of recall and psychomotor impairment produced by benzodiazepines in healthy human volunteers.
The duration and degree of reversal of benzodiazepine effects are related to the dose and plasma concentrations of flumazenil as shown in the following data from a study in normal volunteers.

Magnitude and Duration of Reversal of Sedation as a Function of Flumazenil Dose*
Flumazenil doses of 0.2, 0.6 & 1.0 mg
(blood level in ng/mL)



*Sedation produced by midazolam infusion at a rate of 0.06 - 0.20 mg/kg/hr in healthy volunteers

Generally, doses of approximately 0.1 to 0.2 mg (corresponding to peak plasma levels of 3 to 6 ng/mL) produce partial antagonism, whereas higher doses of 0.4 to 1.0 mg (peak plasma levels of 12 to 28 ng/mL) usually produce complete antagonism in patients who have received the usual sedating doses of benzodiazepines. The onset of reversal is usually evident within 1 to 2 minutes after the injection is completed. Eighty percent response will be reached within 3 minutes, with the peak effect occurring at 6 to 10 minutes. The duration and degree of reversal are related to the plasma concentration of the sedating benzodiazepine as well as the dose of MAZICON given.
In healthy volunteers, MAZICON did not alter intraocular pressure when given alone and reversed the decrease in intraocular pressure seen after administration of midazolam.
PHARMACOKINETICS: After IV administration, plasma concentrations of flumazenil follow a two compartment open pharmacokinetic model with an initial distribution half-life of 7 to 15 minutes and a terminal half-life of 41 to 79 minutes. Peak concentrations of flumazenil are proportional to dose, with an apparent initial volume of distribution of 0.5 L/kg. After redistribution the apparent volume of distribution (V_{ss}) ranges from 0.77 to 1.60 L/kg. Protein binding is approximately 50% and the drug shows no preferential partitioning into red blood cells. Flumazenil is a highly extracted drug. Clearance of flumazenil occurs primarily by hepatic metabolism and is dependent on hepatic blood flow. In pharmacokinetic studies of normal volunteers, total clearance ranges from 0.7 to 1.3 L/hr/kg, with less than 1% of the administered dose eliminated unchanged in the urine. The major metabolites of flumazenil identified in urine are the de-ethylated free acid and its glucuronide conjugate. In preclinical studies there was no evidence of pharmacologic activity exhibited by the de-ethylated free acid. Elimination of radiolabelled drug is essentially complete within 72 hours, with 90% to 95% of the radioactivity appearing in urine and 5% to 10% in the feces.

Pharmacokinetic Parameters Following a 5-minute Infusion of a total of 1.0 mg of MAZICON Mean (Coefficient of variation, Range)

C_{max} (ng/mL)	24 (38%, 11-43)
AUC (ng•hr/mL)	15 (22%, 10-22)
V_{ss} (L/kg)	1 (24%, 0.8-1.6)
Cl (L/hr/kg)	1 (20%, 0.7-1.4)
Half-life (min)	54 (21%, 41-79)

The pharmacokinetics of flumazenil are not significantly affected by gender, age, renal failure (creatinine clearance <10 mL/min), or hemodialysis beginning 1 hour after drug administration. Mean total clearance is decreased to 40% to 60% of normal in patients with moderate liver dysfunction and to 25% of normal in patients with severe liver dysfunction compared with age-matched healthy subjects. This results in a prolongation of the half-life from 0.8 hours in healthy subjects to 1.3 hours in patients with moderate hepatic impairment and 2.4 hours in severely impaired patients. Ingestion of food during an intravenous infusion of the drug results in a 50% increase in clearance, most likely due to the increased hepatic blood flow that accompanies a meal. The pharmacokinetic profile of flumazenil is unaltered in the presence of benzodiazepine agonists and the kinetic profiles of those benzodiazepines are unaltered by flumazenil.

CLINICAL TRIALS: MAZICON has been administered to reverse the effects of benzodiazepines in conscious sedation, general anesthesia, and the management of suspected benzodiazepine overdose.
CONSCIOUS SEDATION: MAZICON was studied in four trials in 970 patients who received an average of 30 mg diazepam or 10 mg midazolam for sedation (with or without a narcotic) in conjunction with both inpatient and outpatient diagnostic or surgical procedures. MAZICON was effective in reversing the sedating and psychomotor effects of the benzodiazepine, however, amnesia was less completely and less consistently reversed. In these studies, MAZICON was administered as an initial dose of 0.4 mg I.V. (two doses of 0.2 mg) with additional 0.2 mg doses as needed to achieve complete awakening, up to a maximum total dose of 1.0 mg. Seventy-eight percent of patients receiving flumazenil responded by becoming completely alert. Of those patients, approximately half responded to doses of 0.4 to 0.6 mg, while the other half responded to doses of 0.8 to 1.0 mg. Adverse effects were infrequent in patients who received 1 mg of MAZICON or less, although injection site pain, agitation and anxiety did occur. Reversal of sedation was not associated with any increase in the frequency of inadequate analgesia or increase in narcotic demand in these studies. While most patients remained alert throughout the 3 hour post-procedure observation period, resedation was observed to occur in 3% to 9% of the patients, and was most common in patients who had received high doses of benzodiazepine. (See PRECAUTIONS.)
GENERAL ANESTHESIA: MAZICON was studied in four trials in 644 patients who received midazolam as an induction and/or maintenance agent in both balanced and inhalational anesthesia. Midazolam was generally administered in doses ranging from 5 to 80 mg, alone and/or in conjunction with muscle relaxants, nitrous oxide, regional or local anesthetics, narcotics and/or inhalational anesthetics. Flumazenil was given as an initial dose of 0.2 mg IV, with additional 0.2 mg doses as needed to reach a complete response, up to a maximum total dose of 1.0 mg. These doses were effective in reversing sedation and restoring psychomotor function, but did not completely restore memory as tested by picture recall. MAZICON was not as effective in the reversal of sedation in patients who had received multiple anesthetic agents in addition to benzodiazepines.
Eighty-one percent of patients sedated with midazolam responded to flumazenil by becoming completely alert or just slightly drowsy. Of those patients, 36% responded to doses of 0.4 to 0.6 mg, while 64% responded to doses of 0.8 to 1.0 mg.
Resedation in patients who responded to MAZICON occurred in 10% to 15% of patients studied and was more common with larger doses of midazolam (>20 mg), long procedures (>60 minutes) and use of neuromuscular blocking agents. (See PRECAUTIONS.)
MANAGEMENT OF SUSPECTED BENZODIAZEPINE OVERDOSE: MAZICON was studied in two trials in 497 patients who were presumed to have taken an overdose of a benzodiazepine, either alone or in combination with a variety of other agents. In these trials, 299 patients were proven to have taken a benzodiazepine as part of the overdose, and 80% of the 148 who received MAZICON responded by an improvement in level of consciousness. Of the patients who responded to flumazenil, 75% responded to a total dose of 1.0 to 3.0 mg. Reversal of sedation was associated with an increased frequency of symptoms of CNS excitation. Of the

patients treated with flumazenil, 1% to 3% were treated for agitation or anxiety. Serious side effects were uncommon, but six seizures were observed in 446 patients treated with flumazenil in these studies. Four of these 6 patients had ingested a large dose of cyclic antidepressants, which increased the risk of seizures. (See WARNINGS.)

INDIVIDUALIZATION OF DOSAGE: GENERAL PRINCIPLES: The serious adverse effects of MAZICON are related to the reversal of benzodiazepine effects. Using more than the minimally effective dose of MAZICON is tolerated by most patients but may complicate the management of patients who are physically dependent on benzodiazepines or patients who are depending on benzodiazepines for therapeutic effect (such as suppression of seizures in cyclic antidepressant overdose).
In high-risk patients, it is important to administer the smallest amount of MAZICON that is effective. The 1-minute wait between individual doses in the dose-titration recommended for general clinical populations may be too short for high risk patients. This is because it takes 6 to 10 minutes for any single dose of flumazenil to reach full effects. Practitioners should slow the rate of administration of MAZICON administered to high risk patients as recommended below.
ANESTHESIA AND CONSCIOUS SEDATION: MAZICON is well tolerated at the recommended doses in individuals who have no tolerance to (or dependence on) benzodiazepines. The recommended dosages and titration rates in anesthesia and conscious sedation (0.2 to 1.0 mg given at 0.2 mg/min) are well tolerated in patients receiving the drug for reversal of a single benzodiazepine exposure in most clinical settings (see Adverse Events). The major risk will be resedation because the duration of effect of a long-acting (or large dose of a short-acting) benzodiazepine may exceed that of MAZICON. Resedation may be treated by giving a repeat dose at no less than 20-minute intervals. For repeat treatment, no more than 1.0 mg (at 0.2 mg/min doses) should be given at any one time and no more than 3.0 mg should be given in any one hour.
OVERDOSE PATIENTS: The risk of confusion, agitation, emotional lability and perceptual distortion with the doses recommended in patients with benzodiazepine overdose (3 to 5 mg administered as 0.5 mg/min) may be greater than that expected with lower doses and slower administration. The recommended doses represent a compromise between a desirable slow awakening and the need for prompt response and a persistent effect in the overdose situation. If circumstances permit, the physician may elect to use the 0.2 mg/minute titration rate to slowly awaken the patient over 5 to 10 minutes, which may help to reduce signs and symptoms on emergence.
MAZICON has no effect in cases where benzodiazepines are not responsible for sedation. Once doses of 3 to 5 mg have been reached without clinical response, additional MAZICON is likely to have no effect.
PATIENTS TOLERANT TO BENZODIAZEPINES: MAZICON may cause benzodiazepine withdrawal symptoms in individuals who have been taking benzodiazepines long enough to have some degree of tolerance. Patients who had been taking benzodiazepines prior to entry into the MAZICON trials who were given flumazenil in doses over 1 mg experienced withdrawal-like events 2 to 5 times more frequently than patients who received less than 1 mg.
In patients who may have tolerance to benzodiazepines, as indicated by clinical history or by the need for larger than usual doses of benzodiazepine, slower titration rates of 0.1 mg/min and lower total doses may help reduce the frequency of emergent confusion and agitation. In such cases special care must be taken to monitor the patients for resedation because of the lower doses of MAZICON used.
PATIENTS PHYSICALLY DEPENDENT ON BENZODIAZEPINES: MAZICON is known to precipitate withdrawal seizures in patients who are physically dependent on benzodiazepines, even if such dependence was established in a relatively few days of high dose sedation in Intensive Care Unit environments. The risk of either seizures or resedation in such cases is high and patients have experienced seizures before regaining consciousness. MAZICON should be used in such settings with extreme caution, since the use of flumazenil in this situation has not been studied and no information as to dose and rate of titration is available. MAZICON should be used in such patients only if the potential benefits of using the drug outweigh the risks of precipitated seizures. Physicians are directed to the scientific literature for the most current information in this area.

INDICATIONS AND USAGE: MAZICON is indicated for the complete or partial reversal of the sedative effects of benzodiazepines in cases where general anesthesia has been induced and/or maintained with benzodiazepines, where sedation has been produced with benzodiazepines for diagnostic and therapeutic procedures, and for the management of benzodiazepine overdose.

CONTRAINDICATIONS: MAZICON is contraindicated:

- In patients with a known hypersensitivity to flumazenil or to benzodiazepines.
- In patients who have been given a benzodiazepine for control of a potentially life-threatening condition (*e.g.* control of intracranial pressure or status epilepticus).
- In patients who are showing signs of serious cyclic antidepressant overdose. (See WARNINGS.)

WARNINGS:

THE USE OF MAZICON HAS BEEN ASSOCIATED WITH THE OCCURRENCE OF SEIZURES.
THESE ARE MOST FREQUENT IN PATIENTS WHO HAVE BEEN ON BENZODIAZEPINES FOR LONG-TERM SEDATION OR IN OVERDOSE CASES WHERE PATIENTS ARE SHOWING SIGNS OF SERIOUS CYCLIC ANTIDEPRESSANT OVERDOSE.
PRACTITIONERS SHOULD INDIVIDUALIZE THE DOSAGE OF MAZICON AND BE PREPARED TO MANAGE SEIZURES.

Risk of Seizures: The reversal of benzodiazepine effects may be associated with the onset of seizures in certain high-risk populations. Possible risk factors for seizures include: concurrent major sedative-hypnotic drug withdrawal, recent therapy with repeated doses of parenteral benzodiazepines, myoclonic jerking or seizure activity prior to flumazenil administration in overdose cases, or concurrent cyclic antidepressant poisoning.
MAZICON is not recommended in cases of serious cyclic antidepressant poisoning, as manifested by motor abnormalities (twitching, rigidity, focal seizure), dysrhythmia (wide QRS, ventricular dysrhythmia, heart block), anticholinergic signs (mydriasis, dry mucosa, hypo-peristalsis), and cardiovascular collapse at presentation. In such cases MAZICON should be withheld and the patient should be allowed to remain sedated (with ventilatory and circulatory support as needed) until the signs of antidepressant toxicity have subsided. Treatment with MAZICON has no known benefit to the seriously ill mixed-overdose patient other than reversing sedation and should not be used in cases where seizures (from any cause) are likely.
Most convulsions associated with flumazenil administration require treatment and have been successfully managed with benzodiazepines, phenytoin or barbiturates. Because of the presence of flumazenil, higher than usual doses of benzodiazepines may be required.

HYPOVENTILATION: Patients who have received MAZICON for the reversal of benzodiazepine effects (after conscious sedation or general anesthesia) should be monitored for resedation, respiratory depression, or other residual benzodiazepine effects for an appropriate period (up to 120 minutes) based on the dose and duration of effect of the benzodiazepine employed.
This is because MAZICON has not been established as an effective treatment for hypoventilation due to benzodiazepine administration. The availability of flumazenil does not diminish the need for prompt detection of hypoventilation and the ability to effectively intervene by establishing an airway and assisting ventilation.
MAZICON may not fully reverse postoperative airway problems or ventilatory insufficiency induced by benzodiazepines. In addition, even if MAZICON is initially effective, such problems may recur because the effects of MAZICON wear off before the effects of many benzodiazepines.
Overdose cases should always be monitored for resedation until the patients are stable and resedation is unlikely.

PRECAUTIONS: RETURN OF SEDATION: MAZICON may be expected to improve the alertness of patients recovering from a procedure involving sedation or anesthesia with benzodiazepines, but should not be substituted for an adequate period of post-procedure monitoring. The availability of MAZICON does not reduce the risks associated with the use of large doses of benzodiazepines for sedation.
Patients should be monitored for resedation, respiratory depression (see WARNINGS), or other persistent or recurrent agonist effects for an adequate period of time after administration of MAZICON.
Resedation is least likely in cases where MAZICON is administered to reverse a low dose of a short-acting benzodiazepine (<10 mg midazolam). It is most likely in cases where a large single or cumulative dose of a benzodiazepine has been given in the course of a long procedure along with neuromuscular blocking agents and multiple anesthetic agents.
Profound resedation was observed in 1% to 3% of patients in the clinical studies. In clinical situations where resedation must be prevented, physicians may wish to repeat the initial dose (up to 1 mg of MAZICON given at 0.2 mg/min) at 30 minutes and possibly again at 60 minutes. This dosage schedule, although not studied in clinical trials, was effective in preventing resedation in a pharmacologic study in normal volunteers.
USE IN THE ICU: MAZICON should be used with caution in the Intensive Care Unit because of the increased risk of unrecognized benzodiazepine dependence in such settings. MAZICON may produce convulsions in patients physically dependant on benzodiazepines. (See INDIVIDUALIZATION OF DOSAGE AND WARNINGS.)
Administration of MAZICON to diagnose benzodiazepine-induced sedation in the Intensive Care Unit is not recommended due to the risk of adverse events as described above. In addition, the prognostic significance of a patient's failure to respond to flumazenil in cases confounded by metabolic disorder, traumatic injury, drugs other than benzodiazepines, or any other reasons not associated with benzodiazepine receptor occupancy is not known.

USE IN OVERDOSE: MAZICON is intended as an adjunct to, not as a substitute for, proper management of airway, assisted breathing, circulatory access and support, internal decontamination by lavage and charcoal, and adequate clinical evaluation.

Necessary measures should be instituted to secure airway, ventilation and intravenous access prior to administering flumazenil. Upon arousal patients may attempt to withdraw endotracheal tubes and/or intravenous lines as the result of confusion and agitation following awakening.

HEAD INJURY: MAZICON should be used with caution in patients with head injury as it may be capable of precipitating convulsions or altering cerebral blood flow in patients receiving benzodiazepines. It should be used only by practitioners prepared to manage such complications should they occur.

USE WITH NEUROMUSCULAR BLOCKING AGENTS: MAZICON should not be used until the effects of neuromuscular blockade have been fully reversed.

USE IN PSYCHIATRIC PATIENTS: MAZICON has been reported to provoke panic attacks in patients with a history of panic disorder.

PAIN ON INJECTION: To minimize the likelihood of pain or inflammation at the injection site, MAZICON should be administered through a freely flowing intravenous infusion into a large vein. Local irritation may occur following extravasation into perivascular tissues.

USE IN RESPIRATORY DISEASE: The primary treatment of patients with serious lung disease who experience serious respiratory depression due to benzodiazepines should be appropriate ventilatory support (See PRECAUTIONS) rather than the administration of MAZICON. Flumazenil is capable of partially reversing benzodiazepine-induced alterations in ventilatory drive in healthy volunteers, but has not been shown to be clinically effective.

USE IN CARDIOVASCULAR DISEASE: MAZICON did not increase the work of the heart when used to reverse benzodiazepines in cardiac patients when given at a rate of 0.1 mg/min in total doses of less than 0.5 mg in studies reported in the clinical literature. Flumazenil alone had no significant effects on cardiovascular parameters when administered to patients with stable ischemic heart disease.

USE IN LIVER DISEASE: The clearance of MAZICON is reduced to 40% to 60% of normal in patients with mild to moderate hepatic disease and to 25% of normal in patients with severe hepatic dysfunction. (See PHARMACOKINETICS.) While the dose of flumazenil used for initial reversal of benzodiazepine effects is not affected, repeat doses of the drug in liver disease should be reduced in size or frequency.

USE IN DRUG AND ALCOHOL DEPENDENT PATIENTS: MAZICON should be used with caution in patients with alcoholism and other drug dependencies due to the increased frequency of benzodiazepine tolerance and dependence observed in these patient populations.

MAZICON is not recommended either as a treatment for benzodiazepine dependence or for the management of protracted benzodiazepine abstinence syndromes, as such use has not been studied.

The administration of flumazenil can precipitate benzodiazepine withdrawal in animals and man. This has been seen in healthy volunteers treated with therapeutic doses of oral lorazepam for up to 2 weeks who exhibited effects such as hot flushes, agitation and tremor when treated with cumulative doses of up to 3 mg doses of flumazenil.

Similar adverse experiences suggestive of flumazenil precipitation of benzodiazepine withdrawal have occurred in some patients in clinical trials. Such patients had a short-lived syndrome characterized by dizziness, mild confusion, emotional lability, agitation (with signs and symptoms of anxiety), and mild sensory distortions. This response was dose-related, most common at doses above 1 mg, rarely required treatment other than reassurance and was usually short lived. When required (5 to 10 cases), these patients were successfully treated with usual doses of a barbiturate, a benzodiazepine, or other sedative drug.

Practitioners should assume that flumazenil administration may trigger dose-dependent withdrawal syndromes in patients with established physical dependence on benzodiazepines and may complicate the management of withdrawal syndromes for alcohol, barbiturates and cross-tolerant sedatives.

DRUG INTERACTIONS: Interaction with central nervous system depressants other than benzodiazepines has not been specifically studied; however, no deleterious interactions were seen when MAZICON was administered after narcotics, inhalational anesthetics, muscle relaxants and muscle relaxant antagonists administered in conjunction with sedation or anesthesia.

Particular caution is necessary when using MAZICON in cases of mixed drug overdosage since the toxic effects (such as convulsions and cardiac dysrhythmias) of other drugs taken in overdose (especially cyclic antidepressants) may emerge with the reversal of the benzodiazepine effect by flumazenil. (See WARNINGS.)

The pharmacokinetics of benzodiazepines are unaltered in the presence of flumazenil.

USE IN AMBULATORY PATIENTS: The effects of MAZICON may wear off before a long-acting benzodiazepine is completely cleared from the body. In general, if a patient shows no signs of sedation within 2 hours after a 1.0 mg dose of flumazenil, serious resedation at a later time is unlikely. An adequate period of observation must be provided for any patient in whom either long-acting benzodiazepines (such as diazepam) or large doses of short-acting benzodiazepines (such as >10 mg of midazolam) have been used. (See INDIVIDUALIZATION OF DOSAGE.)

Because of the increased risk of adverse reactions in patients who have been taking benzodiazepines on a regular basis, it is particularly important that physicians query carefully about benzodiazepine, alcohol and sedative use as part of the history prior to any procedure in which the use of MAZICON is planned. (See DRUG AND ALCOHOL DEPENDENT PATIENTS.)

INFORMATION FOR PATIENTS: MAZICON does not consistently reverse amnesia. Patients cannot be expected to remember information told to them in the post-procedure period and instructions given to patients should be reinforced in writing or given to a responsible family member. Physicians are advised to discuss with their patients, both before surgery and at discharge, that although the patient may feel alert at the time of discharge, the effects of the benzodiazepine may recur. As a result, the patient should be instructed, preferably in writing, that their memory and judgment may be impaired and specifically advised:

1. Not to engage in any activities requiring complete alertness, and not to operate hazardous machinery or a motor vehicle until at least 18 to 24 hours after discharge, and it is certain no residual sedative effects of the benzodiazepine remain.
2. Not to take any alcohol or non-prescription drugs for 18 to 24 hours after flumazenil administration or if the effects of the benzodiazepine persist.

LABORATORY TESTS: No specific laboratory tests are recommended to follow the patient's response or to identify possible adverse reactions.

DRUG/LABORATORY TEST INTERACTIONS: The possible interaction of flumazenil with commonly used laboratory tests has not been evaluated.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Carcinogenesis: No studies in animals to evaluate the carcinogenic potential of flumazenil have been conducted.

Mutagenesis: No evidence for mutagenicity was noted in the Ames test using five different tester strains. Assays for mutagenic potential in *S. cerevisiae* D7 and in Chinese hamster cells were considered to be negative as were blastogenesis assays *in vitro* in peripheral human lymphocytes and *in vivo* in a mouse micronucleus assay. Flumazenil caused a slight increase in unscheduled DNA synthesis in rat hepatocyte culture at concentrations which were also cytotoxic; no increase in DNA repair was observed in male mouse germ cells in an *in vivo* DNA repair assay.

Impairment of fertility: A reproduction study in male and female rats did not show any impairment of fertility at oral dosages of 125 mg/kg/day. From the available data on the area under the curve (AUC) in animals and man the dose represented 120 x the human exposure from a maximum recommended intravenous dose of 5 mg.

PREGNANCY: CATEGORY C. There are no adequate and well-controlled studies of the use of flumazenil in pregnant women. Flumazenil should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Teratogenic Effects: Flumazenil has been studied for teratogenicity in rats and rabbits following oral treatments of up to 150 mg/kg/day. The treatments during the major organogenesis were on days 6 to 15 of gestation in the rat and days 6 to 18 of gestation in the rabbit. No teratogenic effects were observed in rats or rabbits at 150 mg/kg; the dose, based on the available data on the area under the plasma concentration-time curve (AUC) represented 120 x to 600 x the human exposure from a maximum recommended intravenous dose of 5 mg in humans. In rabbits, embryocidal effects (as evidenced by increased pre-implantation and post-implantation losses) were observed at 50 mg/kg or 200 x the human exposure from a maximum recommended intravenous dose of 5 mg. The no-effect dose of 15 mg/kg in rabbits represents 60 x the human exposure.

Nonteratogenic Effects: An animal reproduction study was conducted in rats at oral dosages of 5, 25 and 125 mg/kg/day of flumazenil. Pup survival was decreased during the lactating period, pup liver weight at weaning was increased for the high-dose group (125 mg/kg/day) and incisor eruption and ear opening in the offspring were delayed; the delay in ear opening was associated with a delay in the appearance of the auditory startle response. No treatment-related adverse effects were noted for the other dose groups. Based on the available data from AUC, the effect level (125 mg/kg), represents 120 x the human exposure from 5 mg, the maximum recommended intravenous dose in humans. The no-effect level represents 24 x the human exposure from an intravenous dose of 5 mg.

LABOR AND DELIVERY: The use of MAZICON to reverse the effects of benzodiazepines used during labor and delivery is not recommended because the effects of the drug in the newborn are unknown.

NURSING MOTHERS: Caution should be exercised when deciding to administer MAZICON to a nursing woman because it is not known whether flumazenil is excreted in human milk.

PEDIATRIC USE: MAZICON is not recommended for use in children (either for the reversal of sedation, the management of overdose or the resuscitation of the newborn), as no clinical studies have been performed to determine the risks, benefits and dosages to be used.

GERIATRIC USE: The pharmacokinetics of flumazenil have been studied in the elderly and are not significantly different from younger patients. Several studies of MAZICON in patients over the age of 65 and one study in patients over the age of 80 suggest that while the doses of benzodiazepine used to induce sedation should be reduced, ordinary doses of MAZICON may be used for reversal.

ADVERSE REACTIONS: SERIOUS ADVERSE REACTIONS: Deaths have occurred in patients who received MAZICON in a variety of clinical settings. The majority of deaths occurred in patients with serious underlying disease or in patients who had ingested large amounts of non-benzodiazepine drugs, (usually cyclic antidepressants) as part of an overdose.

Serious adverse events have occurred in all clinical settings, and convulsions are the most common serious adverse event reported. MAZICON administration has been associated with the onset of convulsions in patients who are relying on benzodiazepine effects to control seizures, are physically dependent on benzodiazepines, or who have ingested large doses of other drugs. (See WARNINGS.)

Two of the 446 patients who received MAZICON in controlled clinical trials for the management of a benzodiazepine overdosage had cardiac dysrhythmias (1 ventricular tachycardia, 1 junctional tachycardia).

ADVERSE EVENTS IN CLINICAL STUDIES: The following adverse reactions were considered to be related to MAZICON administration (both alone and for the reversal of benzodiazepine effects) and were reported in studies involving 1875 individuals who received flumazenil in controlled trials. Adverse events most frequently associated with flumazenil alone were limited to dizziness, injection site pain, increased sweating, headache and abnormal or blurred vision (3% to 9%).

BODY AS A WHOLE: Fatigue (asthenia, malaise), Headache, Injection Site Pain*, Injection Site Reaction (thrombophlebitis, skin abnormality, rash)

CARDIOVASCULAR SYSTEM: Cutaneous vasodilation (sweating, flushing, hot flushes)

DIGESTIVE SYSTEM: Nausea and Vomiting (11%)

NERVOUS SYSTEM: Agitation (anxiety, nervousness, dry mouth, tremor, palpitations, insomnia, dyspnea, hyperventilation)*, Dizziness (vertigo, ataxia) (10%), Emotional lability (crying abnormal, depersonalization, euphoria, increased tears, depression, dysphoria, paranoia).

SPECIAL SENSES: Abnormal Vision (visual field defect, diplopia), Paresthesia (sensation abnormal, hypoesthesia)

All adverse reactions occurred in 1% to 3% of cases unless otherwise marked.

*indicates reaction in 3% to 9% of cases.

Observed percentage reported if greater than 9%.

The following adverse events were observed infrequently (less than 1%) in the clinical studies, but were judged as probably related to MAZICON administration and/or reversal of benzodiazepine effects:

NERVOUS SYSTEM: Confusion (difficulty concentrating, delirium), Convulsions (see WARNINGS), Somnolence (stupor).

SPECIAL SENSES: Abnormal Hearing (transient hearing impairment, hyperacusis, tinnitus).

The following adverse events occurred with frequencies less than 1% in the clinical trials. Their relationship to MAZICON administration is unknown, but they are included as alerting information for the physician.

BODY AS A WHOLE: Rigors, shivering.

CARDIOVASCULAR: Arrhythmia (atrial, nodal, ventricular extrasystoles), bradycardia, tachycardia, hypertension, chest pain.

DIGESTIVE SYSTEM: Hiccup.

NERVOUS SYSTEM: Speech disorder (dysphonia, thick tongue).

Not included in this list is operative site pain that occurred with the same frequency in patients receiving placebo as in patients receiving flumazenil for reversal of sedation following a surgical procedure.

DRUG ABUSE AND DEPENDENCE: MAZICON acts as a benzodiazepine antagonist, blocks the effects of benzodiazepines in animals and man, antagonizes benzodiazepine reinforcement in animal models, produces dysphoria in normal subjects, and has had no reported abuse in foreign marketing.

Although MAZICON has a benzodiazepine-like structure it does not act as a benzodiazepine agonist in man and is not a controlled substance.

OVERDOSAGE: Large intravenous doses of MAZICON, when administered to healthy normal volunteers in the absence of a benzodiazepine agonist, produced no serious adverse reactions, severe signs or symptoms, or clinically significant laboratory test abnormalities. In clinical studies, most adverse reactions to flumazenil were an extension of the pharmacologic effects of the drug in reversing benzodiazepine effects.

Reversal with an excessively high dose of MAZICON may produce anxiety, agitation, increased muscle tone, hyperesthesia and possibly convulsions. Convulsions have been treated with barbiturates, benzodiazepines and phenytoin, generally with prompt resolution of the seizures. (See WARNINGS.)

DOSE AND ADMINISTRATION: MAZICON is recommended for intravenous use only. It is compatible with 5% dextrose in water, lactated Ringer's and normal saline solutions. If MAZICON is drawn into a syringe or mixed with any of these solutions, it should be discarded after 24 hours. For optimum sterility, MAZICON should remain in the vial until just before use. As with all parenteral drug products, MAZICON should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

To minimize the likelihood of pain at the injection site, MAZICON should be administered through a freely running intravenous infusion into a large vein.

REVERSAL OF CONSCIOUS SEDATION OR IN GENERAL ANESTHESIA: For the reversal of the sedative effects of benzodiazepines administered for conscious sedation or general anesthesia, the recommended initial dose of MAZICON is 0.2 mg (2 mL) administered intravenously over 15 seconds. If the desired level of consciousness is not obtained after waiting an additional 45 seconds, a further dose of 0.2 mg (2 mL) can be injected and repeated at 60-second intervals where necessary (up to a maximum of 4 additional times) to a maximum total dose of 1 mg (10 mL). The dose should be individualized based on the patient's response, with most patients responding to doses of 0.6 to 1 mg. (See INDIVIDUALIZATION OF DOSAGE.)

In the event of resedation, repeated doses may be administered at 20 minute intervals as needed. For repeat treatment, no more than 1 mg (given as 0.2 mg/min) should be administered at any one time, and no more than 3 mg should be given in any one hour.

It is recommended that MAZICON be administered as the series of small injections described (not as a single bolus injection) to allow the practitioner to control the reversal of sedation to the approximate endpoint desired and to minimize the possibility of adverse effects. (See INDIVIDUALIZATION OF DOSAGE.)

MANAGEMENT OF SUSPECTED BENZODIAZEPINE OVERDOSE: For initial management of a known or suspected benzodiazepine overdose, the recommended initial dose of MAZICON is 0.2 mg (2 mL) administered intravenously over 30 seconds. If the desired level of consciousness is not obtained after waiting 30 seconds, a further dose of 0.3 mg (3 mL) can be administered over another 30 seconds. Further doses of 0.5 mg (5 mL) can be administered over 30 seconds at 1-minute intervals up to a cumulative dose of 3 mg.

Do not rush the administration of MAZICON. Patients should have a secure airway and intravenous access before administration of the drug and be awakened gradually. (See PRECAUTIONS.)

Most patients with benzodiazepine overdose will respond to a cumulative dose of 1-3 mg of MAZICON, and doses beyond 3 mg do not reliably produce additional effects. On rare occasions, patients with a partial response at 3 mg may require additional titration up to a total dose of 5 mg (administered slowly in the same manner).

If a patient has not responded 5 minutes after receiving a cumulative dose of 5 mg MAZICON, the major cause of sedation is likely not to be due to benzodiazepines, and additional MAZICON is likely to have no effect.

In the event of resedation, repeated doses may be given at 20-minute intervals if needed. For repeat treatment, no more than 1 mg (given as 0.5 mg/min) should be given at any one time and no more than 3 mg should be given in any one hour.

SAFETY AND HANDLING: MAZICON is supplied in sealed dosage forms and poses no known risk to the health care provider. Routine care should be taken to avoid aerosol generation when preparing syringes for injection, and spilled medication should be rinsed from the skin with cool water.

HOW SUPPLIED: 5 mL multiple-use vials containing 0.1 mg/mL flumazenil:
Boxes of 10 (NDC 0004-6904-14).
10 mL multiple-use vials containing 0.1 mg/mL flumazenil:
Boxes of 10 (NDC 0004-6905-14).
Store at 59° to 86° F (15° to 30° C).

REVISED: APRIL 1992

Roche Laboratories
a division of Hoffmann-La Roche Inc.

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Be Prepared for Malignant Hyperthermia

Fatalities resulting from malignant hyperthermia are **unexpected, unfair** and almost always, **unnecessary.**

Unexpected because the patient - child or adult - shows no outward signs of this genetic disorder. And there is no simple diagnostic test. Most people have never heard of malignant hyperthermia **until** it strikes.

Unfair because it is triggered by the patient's reaction to certain common anesthetics used during surgery. The life-threatening episode that results has nothing whatsoever to do with the condition requiring the surgery.

Unnecessary, in most cases, because preparedneess and prompt treatment can arrest the episode before it reaches dangerous levels. Persons who know of their susceptibility can have surgery safely using non-triggering anesthetics. When MH strikes unexpectedly during an operation, it can be brought under control by early diagnosis and immediate treatment.

As a medical professional, you can combat this silent killer. For the latest information on diagnosing and treating malignant hyperthermia, contact the Malignant Hyperthermia Association of the United States (MHAUS) at (203) 655-3007. It may mean the difference between life or death.

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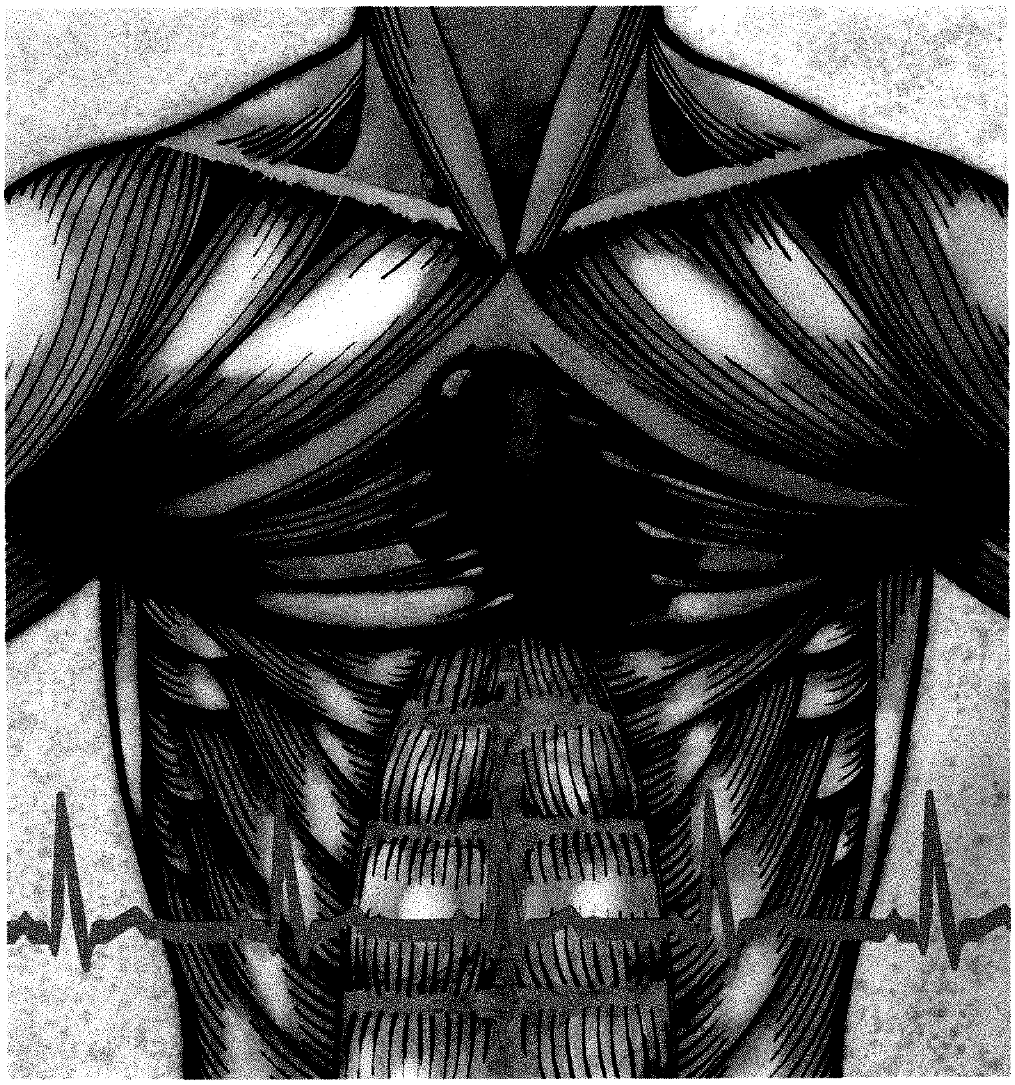
From Burroughs Wellcome Co.
A Long-Acting Neuromuscular Blocker

Excellent
CV Stability



NUROMAX® INJECTION
(doxacurium chloride) 1 mg/mL

Please see brief summary of full prescribing information.

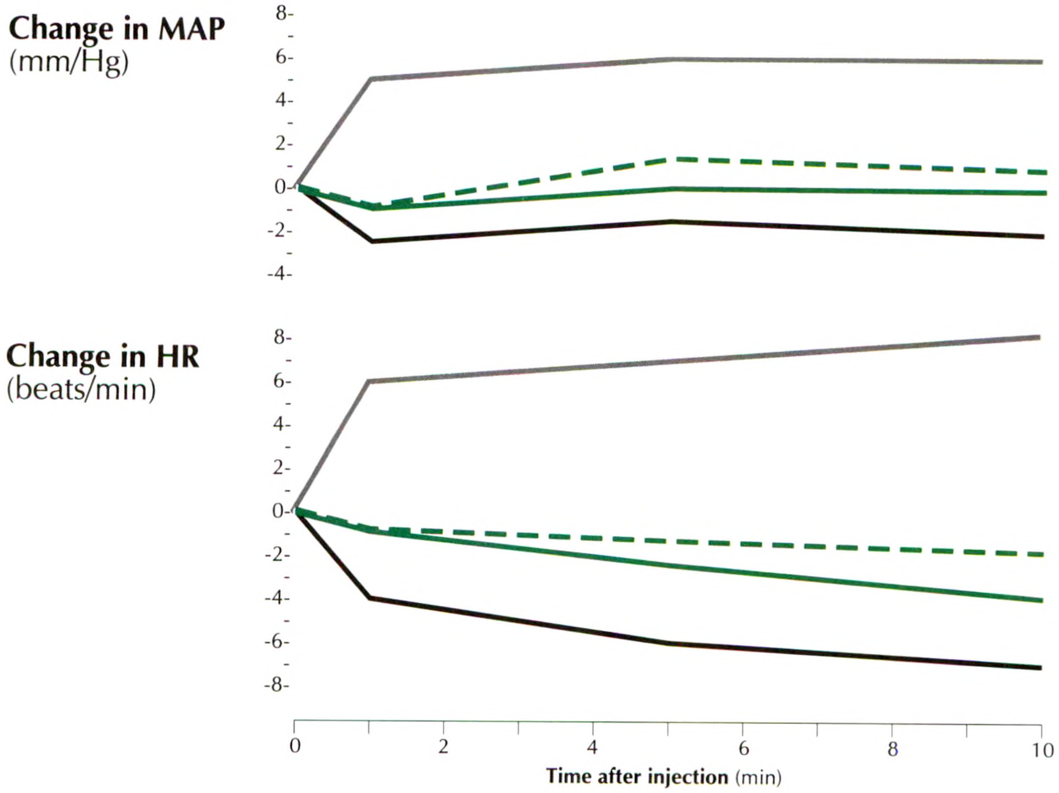
A Long-Acting Neuromuscular Blocker

NUROMAX® INJECTION

(doxacurium chloride)

Excellent CV Stability

Cardiovascular stability comparable with vecuronium

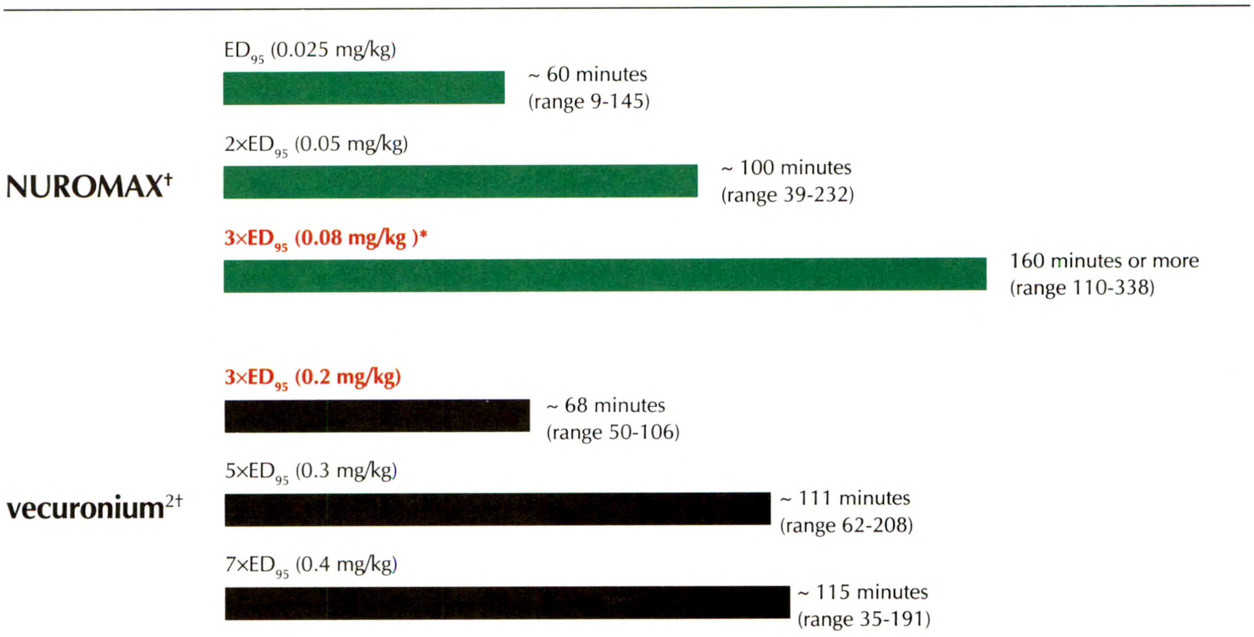


Emmott et al[1] compared the hemodynamic effects of Nuromax 0.037 and 0.075 mg/kg with the effects of pancuronium 0.09 mg/kg and vecuronium 0.075 mg/kg in 36 CABG patients (9 patients, each group).
Mean changes from baseline values of mean systemic arterial pressure (MAP) and heart rate (HR) at 1, 5 and 10 min after administration.
All routine cardiac and vasoactive medications were continued up to the morning of surgery.

▬ ▬ doxacurium 0.037 mg/kg	▬ pancuronium 0.09 mg/kg
▬ doxacurium 0.075 mg/kg	▬ vecuronium 0.075 mg/kg

Longer acting than "high-dose" vecuronium

Clinically effective block (time to 25% recovery)



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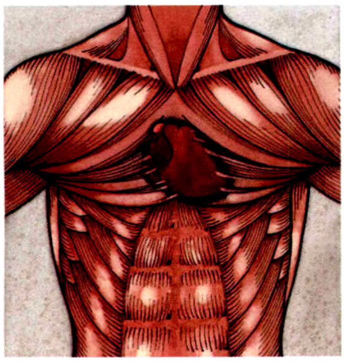
*This dose should be reserved for instances in which a need for very prolonged neuromuscular block is anticipated.

†Numbers shown are not directly comparable since these data have been compiled from different study populations.

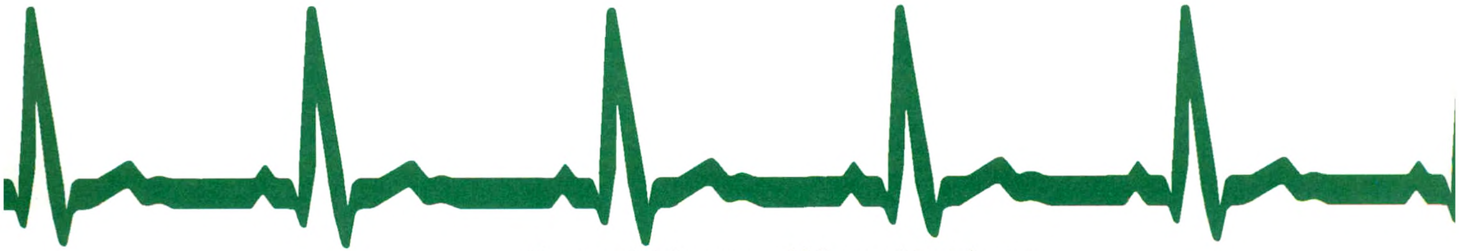
- **Cardiovascular stability comparable with normal saline** [3]
- **Noncumulative**
- **Ready-to-use solution**
- **Vials stored at room temperature, no refrigeration required**
- **Supplied as a 5 mL vial, 1 mg/mL**



NUROMAX® INJECTION

(doxacurium chloride) 1 mg/mL

Excellent for Long CV Procedures



Please see brief summary of full prescribing information

NUROMAX® INJECTION
(DOXACURIUM CHLORIDE)

Brief Summary

This drug should be administered only by adequately trained individuals familiar with its actions, characteristics, and hazards.

Individualization of Dosages: In elderly patients or patients who have impaired renal function, the potential for a prolongation of block may be reduced by decreasing the initial Nuromax dose and by titrating the dose to achieve the desired depth of block. In obese patients (patients weighing $\geq$ 30% more than ideal body weight for height), the Nuromax dose should be determined using the patient's ideal body weight (IBW), according to the following formulae:

Men: IBW in kg = [106 + (6 x inches in height above 5 feet)]/2.2
Women: IBW in kg = [100 + (5 x inches in height above 5 feet)]/2.2

Dosage requirements for patients with severe liver disease are variable; some patients may require a higher than normal initial Nuromax dose to achieve clinically effective block. Once adequate block is established, the clinical duration of block may be prolonged in such patients relative to patients with normal liver function.

As with pancuronium, metocurine, and vecuronium, resistance to Nuromax, manifested by a reduced intensity and/or shortened duration of block, must be considered when Nuromax is selected for use in patients receiving phenytoin or carbamazepine (see **Drug Interactions** subsection of PRECAUTIONS).

As with other nondepolarizing neuromuscular blocking agents, a reduction in dosage of Nuromax must be considered in cachectic or debilitated patients, in patients with neuromuscular diseases, severe electrolyte abnormalities, or carcinomatosis, and in other patients in whom potentiation of neuromuscular block or difficulty with reversal is anticipated. Increased doses of Nuromax may be required in burn patients (see PRECAUTIONS).

INDICATIONS AND USAGE: Nuromax is a long-acting neuromuscular blocking agent, indicated as an adjunct to general anesthesia, to provide skeletal muscle relaxation during surgery. Nuromax can also be used to provide skeletal muscle relaxation for endotracheal intubation.

CONTRAINDICATIONS: Nuromax is contraindicated in patients known to have hypersensitivity to it.

WARNINGS: NUROMAX SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH THE DRUG'S ACTIONS AND THE POSSIBLE COMPLICATIONS OF ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND AN ANTAGONIST ARE WITHIN IMMEDIATE REACH. IT IS RECOMMENDED THAT CLINICIANS ADMINISTERING LONG-ACTING NEUROMUSCULAR BLOCKING AGENTS SUCH AS NUROMAX EMPLOY A PERIPHERAL NERVE STIMULATOR TO MONITOR DRUG RESPONSE, NEED FOR ADDITIONAL RELAXANTS, AND ADEQUACY OF SPONTANEOUS RECOVERY OR ANTAGONISM.

NUROMAX HAS NO KNOWN EFFECT ON CONSCIOUSNESS, PAIN THRESHOLD, OR CEREBRATION. TO AVOID DISTRESS TO THE PATIENT, NEUROMUSCULAR BLOCK SHOULD NOT BE INDUCED BEFORE UNCONSCIOUSNESS.

Nuromax Injection is acidic (pH 3.9 to 5.0) and may not be compatible with alkaline solutions having a pH greater than 8.5 (*e.g.*, barbiturate solutions).

Nuromax Injection contains benzyl alcohol. In newborn infants, benzyl alcohol has been associated with an increased incidence of neurological and other complications which are sometimes fatal. See **Pediatric Use** subsection of PRECAUTIONS.

PRECAUTIONS: General: Nuromax has no clinically significant effects on heart rate; therefore, Nuromax will not counteract the bradycardia produced by many anesthetic agents or by vagal stimulation. Neuromuscular blocking agents may have a profound effect in patients with neuromuscular diseases (*e.g.*, myasthenia gravis and the myasthenic syndrome). In these and other conditions in which prolonged neuromuscular block is a possibility (*e.g.*, carcinomatosis), the use of a peripheral nerve stimulator and a small test dose of Nuromax is recommended to assess the level of neuromuscular block and to monitor dosage requirements. Shorter acting muscle relaxants than Nuromax may be more suitable for these patients.

Resistance to nondepolarizing neuromuscular blocking agents may develop in patients with burns depending upon the time elapsed since the injury and the size of the burn. Nuromax has not been studied in patients with burns. Acid-base and/or serum electrolyte abnormalities may potentiate or antagonize the action of neuromuscular blocking agents. The action of neuromuscular blocking agents may be enhanced by magnesium salts administered for the management of toxemia of pregnancy. Nuromax has not been studied in patients with asthma. No data are available to support the use of Nuromax by intramuscular injection. **Renal and Hepatic Disease:** Nuromax has been studied in patients with end-stage kidney (n=8) or liver (n=7) disease undergoing transplantation procedures (see CLINICAL PHARMACOLOGY). The possibility of prolonged neuromuscular block in patients undergoing renal transplantation and the possibility of a variable onset and duration of neuromuscular block in patients undergoing liver transplantation must be considered when Nuromax is used in such patients. **Obesity:** Administration of Nuromax on the basis of actual body weight is associated with a prolonged duration of action in obese patients (patients weighing $\geq$ 30% more than ideal body weight for height) (see CLINICAL PHARMACOLOGY). Therefore, the dose of Nuromax should be based upon ideal body weight in obese patients (see **Individualization of Dosages** subsection of CLINICAL PHARMACOLOGY). **Malignant Hyperthermia (MH):** In a study of MH-susceptible pigs, Nuromax did not trigger MH. Nuromax has not been studied in MH-susceptible patients. Since MH can develop in the absence of established triggering agents, the clinician should be prepared to recognize and treat MH in any patient scheduled for general anesthesia. **Long-Term Use in the Intensive Care Unit (ICU):** No data are available on the long-term use of Nuromax in patients undergoing mechanical ventilation in the ICU. **Drug Interactions:** Prior administration of succinylcholine has no clinically important effect on the neuromuscular blocking action of Nuromax. The use of Nuromax before succinylcholine to attenuate some of the side effects of succinylcholine has not been studied. There are no clinical data on concomitant use of Nuromax and other nondepolarizing neuromuscular blocking agents. Isoflurane, enflurane and halothane decrease the ED_{50} of Nuromax by 30% to 45%. These agents may also prolong the clinically effective duration of action by up to 25%. Other drugs which may enhance the neuromuscular blocking action of nondepolarizing agents such as Nuromax include certain antibiotics (*e.g.*, aminoglycosides, tetracyclines, bacitracin, polymyxins, lincomycin, clindamycin, colistin, and sodium colistimethate), magnesium salts, lithium, local anesthetics, procainamide, and quinidine. As with some other nondepolarizing neuromuscular blocking agents, the time of onset of neuromuscular block induced by Nuromax is lengthened and the duration of block is shortened in patients receiving phenytoin or carbamazepine. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Carcinogenesis and fertility studies have not been performed. Nuromax was evaluated in a battery of four short-term mutagenicity tests. It was non-mutagenic in the Ames Salmonella assay, in the mouse lymphoma assay, and in the human lymphocyte assay. In the *in vivo* rat bone marrow cytogenetic assay, statistically significant increases in the incidence of structural abnormalities, relative to vehicle controls, were observed in male rats dosed with 0.1 mg/kg (0.625 mg/m^2) Nuromax and sacrificed at 6 hours, but not at 24 or 48 hours, and in female rats dosed with 0.2 mg/kg (1.25 mg/m^2) Nuromax and sacrificed at 24 hours, but not at 6 or 48 hours. There was no increase in structural abnormalities in either male or female rats given 0.3 mg/kg (1.875 mg/m^2) Nuromax and sacrificed at 6, 24, or 48 hours. Thus, the incidence of abnormalities in the *in vivo* rat bone marrow cytogenetic assay was not dose-dependent and, therefore, the likelihood that the observed abnormalities were treatment-related or clinically significant is low. **Pregnancy:** Teratogenic Effects: Pregnancy Category C. Teratology testing in nonventilated, pregnant rats and mice treated subcutaneously with maximum subparalyzing doses of Nuromax revealed no maternal or fetal toxicity or teratogenic effects. There are no adequate and well-controlled studies of Nuromax in pregnant women. Because animal studies are not always predictive of human response and the doses used were subparalyzing, Nuromax should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Labor and Delivery:** The use of Nuromax during labor, vaginal delivery, or cesarean section has not been studied. It is not known whether Nuromax administered to the mother has immediate or delayed effects on the fetus. The duration of action of Nuromax exceeds the usual duration of operative obstetrics (cesarean section). Therefore, Nuromax is not recommended for use in patients undergoing C-section. **Nursing Mothers:** It is not known whether Nuromax is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised following Nuromax administration to a nursing woman. **Pediatric Use:** Nuromax has not been studied in children below the age of 2 years. See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION for clinical experience and recommendations for use in children 2 to 12 years of age. **Geriatric Use:** Nuromax has been used in elderly patients, including patients with significant cardiovascular disease. In elderly patients the onset of maximum block is slower and the duration of neuromuscular block produced by Nuromax is more variable and, in some cases, longer than in young adult patients (see **Pharmacodynamics** and **Individualization of Dosages** subsections of CLINICAL PHARMACOLOGY).

ADVERSE REACTIONS: The most frequent adverse effect of nondepolarizing blocking agents as a class consists of an extension of the pharmacological action beyond the time needed for surgery and anesthesia. This effect may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiratory insufficiency and apnea which require manual or mechanical ventilation until recovery is judged to be clinically adequate (see OVERDOSAGE). Inadequate reversal of neuromuscular block from Nuromax is possible, as with all nondepolarizing agents. Prolonged neuromuscular block and inadequate reversal may lead to postoperative complications. **Observed in Clinical Trials:** Adverse experiences were uncommon among the 1034 surgical patients and volunteers who received Nuromax and other drugs in U.S. clinical studies in the course of a wide variety of procedures conducted during balanced or inhalational anesthesia. The following adverse experiences were reported in patients administered Nuromax (all events judged by investigators during the clinical trials to have a possible causal relationship):

Incidence Greater than 1% - None

Incidence Less than 1% -

Cardiovascular*:	hypotension,† flushing,† ventricular fibrillation, myocardial infarction
Respiratory:	bronchospasm, wheezing
Dermatological:	urticaria, injection site reaction
Special Senses:	diplopia
Nonspecific:	difficult neuromuscular block reversal, prolonged drug effect, fever

* Reports of ventricular fibrillation (n=1) and myocardial infarction (n=1) were limited to ASA Class 3-4 patients undergoing cardiac surgery (n=142).

† 0.3% incidence. All other reactions unmarked were $\leq$ 0.1%.

OVERDOSAGE: Overdosage with neuromuscular blocking agents may result in neuromuscular block beyond the time needed for surgery and anesthesia. The primary treatment is maintenance of a patent airway and controlled ventilation until recovery of normal neuromuscular function is assured. Once evidence of recovery from neuromuscular block is observed, further recovery may be facilitated by administration of an anticholinesterase agent (*e.g.*, neostigmine, edrophonium) in conjunction with an appropriate anticholinergic agent (see **Antagonism of Neuromuscular Block**).

Antagonism of Neuromuscular Block: ANTAGONISTS (SUCH AS NEOSTIGMINE) SHOULD NOT BE ADMINISTERED PRIOR TO THE DEMONSTRATION OF SOME SPONTANEOUS RECOVERY FROM NEUROMUSCULAR BLOCK. THE USE OF A NERVE STIMULATOR TO DOCUMENT RECOVERY AND ANTAGONISM OF NEUROMUSCULAR BLOCK IS RECOMMENDED. T_4/T_1 SHOULD BE > ZERO BEFORE ANTAGONISM IS ATTEMPTED.

In an analysis of patients in whom antagonism of neuromuscular block was evaluated following administration of single doses of neostigmine averaging 0.06 mg/kg (range: 0.05 to 0.075) administered at approximately 25% T_1 spontaneous recovery during balanced anesthesia, 71% of patients exhibited $T_4/T_1 \geq 0.7$ before monitoring was discontinued. For these patients, the mean time to $T_4/T_1 \geq 0.7$ was 19 minutes (range: 7 to 55). As with other long-acting nondepolarizing neuromuscular blocking agents, the time for recovery of neuromuscular function following administration of neostigmine is dependent upon the level of residual neuromuscular block at the time of attempted reversal; longer recovery times than those cited above may be anticipated when neostigmine is administered at more profound levels of block (*i.e.*, at < 25% T_1 recovery).

Patients should be evaluated for adequate clinical evidence of antagonism, *e.g.*, 5-second head lift, and grip strength. Ventilation must be supported until no longer required. As with other neuromuscular blocking agents, physicians should be alert to the possibility that the action of the drugs used to antagonize neuromuscular block may wear off before the effects of Nuromax on the neuromuscular junction have declined sufficiently.

Antagonism may be delayed in the presence of debilitation, carcinomatosis, and the concomitant use of certain broad spectrum antibiotics, or anesthetic agents and other drugs which enhance neuromuscular block or separately cause respiratory depression (see **Drug Interactions** subsection of PRECAUTIONS). Under such circumstances the management is the same as that of prolonged neuromuscular block.

In clinical trials, a dose of 1 mg/kg edrophonium was not as effective as a dose of 0.06 mg/kg neostigmine in antagonizing moderate to deep levels of neuromuscular block (i.e., < 60% T_1 recovery). Therefore, the use of 1 mg/kg edrophonium is not recommended for reversal from moderate to deep levels of block. The use of pyridostigmine has not been studied.

Adults: *Initial Doses:* When administered as a component of a thiopental/narcotic induction-intubation paradigm as well as for production of long-duration neuromuscular block during surgery, 0.05 mg/kg (2 x ED_{95}) Nuromax produces good-to-excellent conditions for tracheal intubation in 5 minutes in approximately 90% of patients. Lower doses of Nuromax may result in a longer time for development of satisfactory intubation conditions. Clinically effective neuromuscular block may be expected to last approximately 100 minutes on average (range: 39 to 232) following 0.05 mg/kg Nuromax administered to patients receiving balanced anesthesia.

An initial Nuromax dose of 0.08 mg/kg (3 x ED_{95}) should be reserved for instances in which a need for very prolonged neuromuscular block is anticipated. In approximately 90% of patients, good-to-excellent intubation conditions may be expected in 4 minutes after this dose; however, clinically effective block may be expected to persist for as long as 160 minutes or more (range: 110 to 338) (see CLINICAL PHARMACOLOGY).

STORAGE: Store Nuromax Injection at room temperature of 15° to 25°C (59° to 77°F). DO NOT FREEZE.

U.S. Patent No. 4701460

March 1991 562004

1. Emmott RS, Bracey BJ, Goldhill DR, Yate PM, Flynn PJ. Cardiovascular effects of doxacurium, pancuronium and vecuronium in anaesthetized patients presenting for coronary artery bypass surgery. *Br J Anaesth.* 1990;65:480-486.
2. Tullock WC, Diana P, Cook R, et al. Neuromuscular and cardiovascular effects of high-dose vecuronium. *Anesth Analg.* 1990;70:86-90.
3. Stoops CM, Curtis CA, Kovach DA, et al. Hemodynamic effects of doxacurium chloride in patients receiving oxygen sufentanil anesthesia for coronary artery bypass grafting or valve replacement. *Anesthesiology.* 1988;69:365-370.

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Regional Anesthesia and Pain Management
Section Editor
Phillip O. Bridenbaugh

Pulmonary Function and Stress Response After Laparoscopic Cholecystectomy: Comparison With Subcostal Incision and Influence of Thoracic Epidural Analgesia

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Laurens T. de Wit, MD, Cor J. Kalkman, MD, PhD, and Johannes Oosting, PhD

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Laparoscopic cholecystectomy (LPC) is increasingly used to treat symptomatic cholelithiasis. We compared the effects of cholecystectomy by subcostal incision to those of LPC on lung function and endocrine metabolic response. The effects of thoracic epidural analgesia for LPC were studied as well. Thirty patients undergoing elective cholecystectomy under general anesthesia were allocated to three study groups: group I, cholecystectomy by subcostal incision; group II, LPC; group III, LPC and epidural analgesia with 0.5% bupivacaine with epinephrine, followed by continuous epidural infusion of 6 mL of 0.5% bupivacaine. Forced vital capacity (FVC), peak expiratory flow, and forced expiratory volume in 1 s were measured with the patients in a half-sitting position. In all groups, sustained decreases in FVC, forced expiratory volume in 1 s, and peak expiratory flow were observed up to 24 h after surgery. Reduction of FVC was significantly more in group I compared with groups II and III ($P < 0.05$). The FVC in group I decreased from 3.8 ± 0.42 (SD) to 1.1 ± 0.27 L ($P < 0.01$), in group II from 3.6 ± 1.46 to 2.1 ± 0.94 L ($P < 0.05$), and in group III from 3.8 ± 0.92 to 2.8 ± 0.90 L ($P < 0.05$). In all groups, plasma glucose and cortisol increased after surgery compared with baseline levels ($P < 0.05$). At 240 min after surgery, a small but significant decrease of cortisol was measured in group III ($P < 0.05$). Patients in groups I and II received significantly more fentanyl during surgery and nicomorphine postoperatively compared with patients in group III ($P < 0.05$). In group III, epidural analgesia decreased visual analogue pain scores ($P < 0.05$), but there was no difference in pain scores between groups I and II. In conclusion, the endocrine metabolic response is not abolished after LPC. Thoracic epidural analgesia decreased postoperative pain and possibly attenuated the metabolic endocrine response, but it did not improve lung function after LPC. Nevertheless, pulmonary function is significantly better after LPC than after cholecystectomy via subcostal incision.

(Anesth Analg 1992;75:381–5)

Upper abdominal surgery is associated with postoperative pulmonary dysfunction in up to 48% of patients (1). Impaired diaphragmatic function, type of skin incision, postoperative pain, muscle paralysis, and decreased functional residual capacity have all been found to contribute to postoperative pulmonary dysfunction (2–4). Laparoscopic cholecystectomy (LPC) is a new surgical technique that is rapidly becoming the first choice for management of symptomatic cholelithiasis. The purpose of this study was to compare the effects of LPC with those of cholecystectomy by subcostal incision (CSI) on postoperative pulmonary function.

Because it has been postulated that decreasing or abolishing the metabolic endocrine response to surgery may reduce postoperative morbidity (5,6), we also studied the effects of LPC on the metabolic endocrine response to surgery.

Thoracic epidural analgesia combined with general anesthesia was used to evaluate the influence of pain after LPC on postoperative lung function and metabolic endocrine response.

Methods

The protocol of this study was institutionally approved. Thirty patients (ASA physical status I or II) undergoing elective cholecystectomy under general anesthesia gave informed consent to participate in the study. Patients were assigned to group I and underwent CSI whenever the instrumentation for

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laparoscopic surgery was not available. Patients who underwent a laparoscopic procedure were assigned on an alternating basis to either group II or III. Patients in group II underwent LPC, as described by Dubois et al. (7) and patients in group III LPC under general anesthesia combined with epidural analgesia.

Diazepam (10 mg) was administered orally 1 h before induction of anesthesia. Standard monitoring was used. A radial artery was cannulated percutaneously with a 20-gauge cannula for arterial blood pressure measurement and blood sampling. The infusion regimen consisted of normal saline solution at a rate of 6 $mL \cdot kg^{-1} \cdot h^{-1}$ during the operation and for 4 h thereafter. In group III, a 16-gauge epidural catheter was inserted under local analgesia (5 mL of 1% lidocaine with 5 µg/mL of epinephrine) at T6-8 immediately before the induction of general anesthesia. After insertion of the epidural catheter, 10 mL of 0.5% bupivacaine with 5 µg/mL of epinephrine was injected, and the level of analgesia was confirmed with the pinprick method. In all groups, anesthesia was induced with thiopental (3–5 mg/kg), followed by vecuronium (0.1 mg/kg IV) to facilitate tracheal intubation. Anesthesia was maintained with 1.4% enflurane (inspired concentration) delivered through a Dräger vaporizer and oxygen in air (FIO_2 = 0.5). Ventilation was adjusted to maintain end-tidal CO_2 between 35 and 40 mm Hg. Additional doses of vecuronium were administered to maintain one or two responses to train-of-four stimulation. In groups I and II, fentanyl (5 µg/kg IV) was administered before skin incision. When patients showed signs of insufficient analgesia, such as sweating, lacrimation, or a rise in mean arterial blood pressure or heart rate of >20%, or both, above preinduction levels, fentanyl (0.1 mg IV) was administered, followed by another dose if necessary. For postoperative analgesia, a continuous epidural infusion with 0.5% bupivacaine was started after the completion of surgery at a rate of 5 mL/h in group III patients. Postoperatively, patients in all groups received nicomorphine (10 mg IM) when they complained of pain, followed by another dose if necessary. All patients were confined to bed the first 24 h after surgery and did not receive chest physical therapy, breathing exercises, or incentive spirometry.

Assessments of pulmonary function were made with a commercially available portable respirometer (Dräger Spirotron, Lübeck, Germany). Measurements were made with the patients in a half-sitting position, with the head-up tilt at an angle of 45°. Forced vital capacity (FVC), peak expiratory flow, and forced expiratory volume in 1 s (Fev_1) were recorded the day before surgery and 2, 4, 8, and 24 h after surgery.

For determination of plasma cortisol and glucose, blood samples were obtained after induction of anesthesia, before incision, and at 30, 60, 120, and 240 min. Plasma was obtained by centrifugation and kept frozen at −20°C until required for assay. Cortisol levels were obtained through commercial radioimmunoassay (TDX, Abbott Laboratories, Diagnostic Division, Irving, Tex.). Coefficients of variation for this assay were 12.5% at 0.1 µmol/L, 6.6% at 0.4 µmol/L, and 5.7% at 1.1 µmol/L. Plasma glucose concentrations were analyzed by a routine glucose dehydrogenase method (EPOS Analyser 5060, Eppendorf, Hamburg, Germany). Coefficients of variation for this assay were 2.0% at 5.0 mmol/L and 2.5% at 10.0 mmol/L.

The degree of postoperative pain was assessed with a 0–10-cm visual analogue scale (VAS). Assessments were made when the patients arrived at the recovery ward and at 2, 4, 8, and 24 h.

Results are expressed as mean ± SD. Data were analyzed with one- and two-way analysis of variance for repeated measurements. When indicated, differences between baseline and subsequent means were compared with paired *t*-tests with Bonferroni correction for multiple comparisons. Opioid analgesic requirements and VAS scores were analyzed with the Wilcoxon signed rank test; *P* values <0.05 were considered significant.

Results

Demographic data of the patients in the three study groups are presented in Table 1. The groups were similar with respect to ASA classification, age, height, weight, and duration of the operation.

Ventilatory data are presented in Figure 1. The FVC was decreased in all groups up to 24 h after surgery. In group I, FVC decreased from 3.8 ± 0.42 to

Table 1. Clinical Characteristics in 30 Patients Undergoing Elective Cholecystectomy

	Group I (Subcostal incision) (*n* = 10)	Group II (Laparoscopic surgery) (*n* = 10)	Group III (Laparoscopic surgery combined with epidural analgesia) (*n* = 10)
Weight (kg)	72.0 ± 13.0	68.9 ± 7.6	79.4 ± 13.7
Height (m)	1.64 ± 0.1	1.65 ± 0.9	1.68 ± 0.1
Gender (M/F)	2/8	1/9	1/9
Age (yr)	40.9 ± 9.4	48.4 ± 19.7	49.9 ± 11.6
ASA physical status (I/II)	7/3	4/6	8/2
Duration of operation (min)	78 ± 29.3	90.5 ± 27.0	70.0 ± 20.2

F, female; M, male.
Mean ± SD.

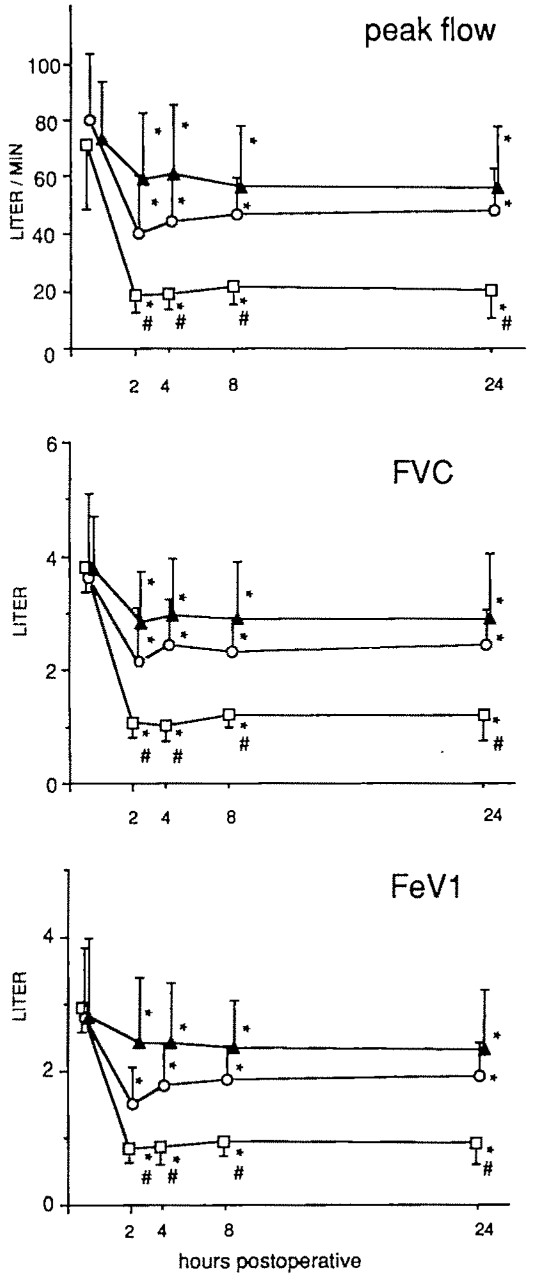

Figure 1. Ventilatory parameters before and after surgery. Values are mean ± SD. #$P < 0.05$ difference between group I (□) and groups II (○) and III (▲). *$P < 0.05$ decrease from preoperative values. Group I, cholecystectomy via subcostal incision; group II, laparoscopic cholecystectomy; group III, laparoscopic cholecystectomy with thoracic epidural analgesia; FVC, forced vital capacity; Fev_1, forced capacity volume in 1 s.

1.1 ± 0.27 L ($P < 0.01$), in group II from 3.6 ± 1.5 to 2.1 ± 0.94 L, and in group III from 3.8 ± 0.92 to 2.8 ± 0.90 L 2 h after surgery ($P < 0.05$). The reduction of FVC was significantly smaller in groups II or III compared with that in the CSI group ($P < 0.05$). Similar ventilatory changes were measured with Fev_1 and peak flow. There were no statistically significant differences between groups II and III. The ratio of Fev_1 to FVC remained unchanged.

Plasma cortisol increased significantly in all three groups compared with baseline levels ($P < 0.05$) (Figure 2). Peak cortisol concentration of 1.12 ± 0.22 μmol/L was reached in group III 120 min after induction of anesthesia. In contrast, maximal levels in groups I and II were reached 240 min after induction of anesthesia (1.23 ± 0.16 and 1.22 ± 0.22 μmol/L, respectively). At that time, cortisol concentration in group III was significantly lower than in groups I and II. Plasma glucose increased significantly in all three groups compared with baseline levels ($P < 0.05$) (Figure 2). Glucose concentrations reached maximal values in group I after 120 min (7.3 ± 0.67 mmol/L) and in group II after 240 min (7.7 ± 1.33 mmol/L). Glucose concentrations were significantly higher in group III at 30 and 60 min after induction compared with those in groups I and II ($P < 0.05$). In group III, a peak glucose level of 8.1 ± 1.59 mmol/L was measured at 60 min.

Opioid analgesic requirements during operation were similar in groups I and II. Patients in groups I and II received a total of 510 ± 184.2 and 510 ± 164.0 μg of fentanyl, respectively. Compared with groups I and II, significantly less fentanyl (265.0 ± 92.3 μg) was administered to patients in group III ($P < 0.05$). During the first 24 h after surgery, two patients in group III each received one dose of nicomorphine intramuscularly. Patients in groups I and II received significantly more nicomorphine during the first 24 h postoperatively ($P < 0.05$). Mean postoperative nicomorphine requirements in group I were 31.5 ± 14.8 mg and in group II 32 ± 17.8 mg. On arrival at the recovery room, VAS scores in group III were significantly lower compared with those of the two other groups ($P < 0.05$) (Figure 3). No significant differences were observed with respect to pain scores between the CSI and LPC groups at any time during the study. After 24 h, there were no significant differences among the three groups.

Discussion

The results of this study indicate that pulmonary function is significantly better after LPC than after CSI during the first 24 h postoperatively. Although we observed significant decreases of FVC after both techniques for cholecystectomy, the decrease of FVC in the laparoscopic groups was only half that of the CSI group. Unfortunately, we were unable to randomize our groups because the instrumentation for laparoscopic surgery was not always available; however, the groups were similar with respect to demographic data, suggesting that failure to randomize our groups did not influence the results of this study.

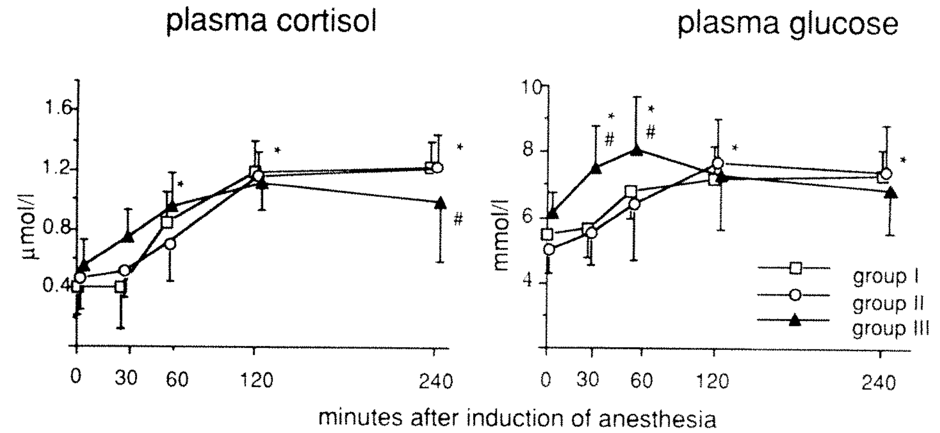

Figure 2. Metabolic endocrine response as measured by plasma cortisol and glucose. Values are mean ± SD. #$P < 0.05$ difference between group III and groups I and II. *$P < 0.05$ increase from preoperative values. Group I, cholecystectomy via subcostal incision; group II, laparoscopic cholecystectomy; group III, laparoscopic cholecystectomy with thoracic epidural analgesia.

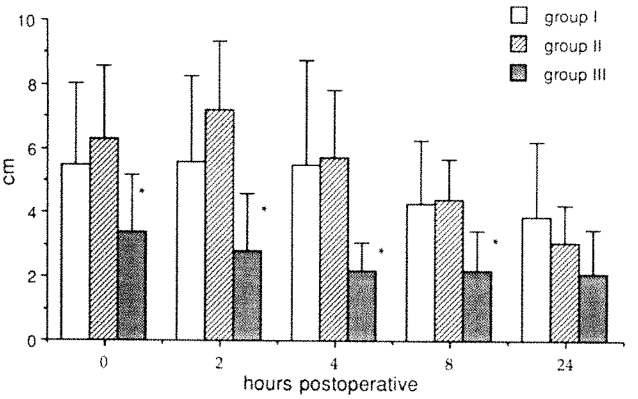

Figure 3. Visual analogue pain scores (0–10 cm) after surgery. *$P < 0.05$ difference between group I or II and group III. Group I, cholecystectomy via subcostal incision; group II, laparoscopic cholecystectomy; group III, laparoscopic cholecystectomy with thoracic epidural analgesia.

Because it has been shown that patients with chronic obstructive pulmonary disease are at risk of developing pulmonary complications after upper abdominal surgery (4), these patients may benefit from laparoscopic surgery. The combination of a general anesthetic technique with thoracic epidural analgesia for LPC did not significantly improve lung function further.

The mechanisms producing pulmonary deterioration after upper abdominal surgery are not completely understood. It appears that the type of incision plays an important role. Becquemin et al. (4) found that a midline incision caused significantly more pulmonary dysfunction than a transverse incision in patients with chronic obstructive pulmonary disease. Others reported that, given the same type of incision, postoperative pulmonary function was significantly better with smaller incisions than with larger ones (2). The data of our study confirm that a small incision results in better pulmonary function, because laparoscopic surgery involves only three minimal incisions.

Some investigators consider pain to be an important determinant of postoperative pulmonary dysfunction (3). However, even with good pain relief, lung function as measured by FVC and Fev_1 decreased to approximately 50%–60% of the preoperative value after abdominal surgery (8). Several studies indicated that epidural analgesia results in an average improvement of lung function of 15% compared with systemic analgesia (9,10). We did not study the effects of epidural analgesia on lung function in patients undergoing CSI. Therefore it is possible that the addition of epidural analgesia in patients with CSI would have resulted in better postoperative pulmonary function. However, even with a 15% improvement of lung function tests in patients undergoing CSI, these values would still be lower than those of patients undergoing LPC. In our study, pain assessments indicated that epidural analgesia improved analgesia in the postoperative period after LPC, but the differences in pulmonary function tests did not reach statistical significance. These findings are in agreement with those of Simonneau et al. (11) who demonstrated considerable postoperative impairment of diaphragmatic function after CSI that was not prevented by epidural analgesia.

A reduction of postoperative pain after laparoscopic surgery was reported by Dubois et al. (7); however, in that study postoperative pain scores were not reported. Our results do not support the contention that postoperative pain is diminished after LPC compared with CSI. The VAS pain scores and opioid analgesic requirements both during operation and postoperatively were not statistically significant between groups I and II. Although we did not assess the level of epidural analgesia postoperatively, we did confirm its effectiveness preoperatively with the pinprick method. In addition, analgesic requirements in the epidural analgesia group were significantly lower during the operation and during the first 24 postoperative hours compared with groups I and II.

Dubois et al. (7) also mentioned a rapid recovery with less surgical trauma after LPC. We expected that the metabolic endocrine response after LPC might be less pronounced than after CSI; however, our data show that the metabolic endocrine response after LPC is not diminished. The rapid recovery of patients after LPC is probably not due to effects of this technique on the metabolic endocrine response.

In a previous report (12), we observed peak levels of glucose and cortisol 150 min after CSI. Therefore we expected that in all groups, peak levels of cortisol would have been reached within 4 h after surgery. Data of this study show that there is a slight attenuation of the metabolic endocrine response in patients who received epidural analgesia, which becomes apparent 2 h after surgery. Because there are no data after 240 min, it is unclear whether this is a true diverging trend. Kehlet (5) could not demonstrate an effect of epidural analgesia on the metabolic endocrine response after major upper abdominal procedures. The higher glucose levels in the epidural group at 30 and 60 min are unexplained. High levels of catecholamines are known to produce higher glucose levels. Anxiety experienced by some patients during insertion of the epidural catheter or, alternatively, the resorption of the epinephrine from the local analgesic may have led to higher levels of cathecholamines. This may have resulted in higher glucose levels.

In conclusion, the endocrine metabolic response to surgery is not abolished after LPC under general anesthesia. Pulmonary function is significantly better after LPC than after CSI. There is no difference in pain after both surgical techniques. Thoracic epidural analgesia for laparoscopic surgery provides adequate pain relief but does not improve lung function after LPC.

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Interscalene Brachial Plexus Block for Shoulder Surgery: A Proximal Paresthesia Is Effective

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This study was designed to determine whether the location of paresthesias is related to the success of interscalene blocks in providing anesthesia for shoulder surgery. Interscalene blocks were performed in 45 patients presenting for elective shoulder surgery. Interscalene injections of 33–55 mL of 1.5% mepivacaine with epinephrine were performed after the first elicited paresthesia to the shoulder, arm, forearm, or hand. In 20 patients (45%), the initial elicited paresthesia was to the shoulder, whereas in 25 patients (55%), the first parethesia was reported as distal to the shoulder. All patients developed brachial plexus anesthesia adequate for shoulder surgery. The time-course of onset of motor block as evaluated at the shoulder and elbow was not different between patients with shoulder paresthesias and those with more distal paresthesias. Handgrip strength was quantitatively evaluated with a dynamometer, and both paresthesia groups showed similar decrements in hand strength except at the end of the measurement period, when patients with distal paresthesias had a significantly weaker handgrip than patients with shoulder paresthesias. We recommend that paresthesias to the shoulder be accepted in performing interscalene blocks for patients undergoing shoulder surgery.

(Anesth Analg 1992;75:386–8)

The interscalene brachial plexus block is a widely used anesthetic technique for surgery of the shoulder and upper arm. In our experience, when this block is performed at the level of C-6, the earliest elicited paresthesia is often to the shoulder. It has been recommended widely in texts of regional anesthesia that shoulder paresthesias not be accepted as an indication that the needle tip is near the plexus and that further needle probing should be performed until a more distal paresthesia is achieved (1–4). Prolonged needle exploration in the neck in search of a distal paresthesia not only delays completion of the block but also may add significantly to patient discomfort. This investigation was undertaken to prospectively evaluate the relative success of interscalene block for shoulder surgery by means of a shoulder versus a more distal first-reported paresthesia.

Methods

After institutional approval, 45 unpremedicated patients (aged 17–79 yr) presenting for shoulder surgery were studied. Written, informed consent was obtained from all patients. Interscalene block was performed at the level of C-6 with a 23-gauge, 2.5-cm needle using a paresthetic technique described previously by Winnie (5). Patients were instructed to verbally identify the site of paresthesia as toward the shoulder, upper arm, elbow, forearm, or hand. At the first elicited paresthesia to the shoulder or more distally, patients received a standardized dose (10 mg/kg) of bicarbonated 1.5% mepivacaine with epinephrine (3 μg/mL). A paresthesia to the shoulder was classified as "proximal," whereas a paresthesia to the upper arm, elbow, forearm, or hand was classified as "distal."

Motor block was assessed by evaluating the patient's ability to elevate the upper arm at the shoulder, flex the forearm at the elbow, and perform a handgrip maneuver at baseline and every 2 min for 16 min after the interscalene injection. Motor block at the shoulder and elbow was qualitatively evaluated with a four-point scale: baseline motor ability was rated as grade 3; some demonstrable weakness was rated grade 2; marked weakness but with some retained antigravity ability was rated grade 1; and complete loss of antigravity ability was rated grade 0. Handgrip strength was quantitatively evaluated in all patients with a JAMAR dynamometer (JAMAR model 2A3, Asimow Engineering Co., Santa Monica, Calif.).

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Table 1. Surgical Procedures Performed in 45 Patients Undergoing Elective Shoulder Surgery

	Proximal paresthesia group	Distal paresthesia group
Open procedures		
Stabilization	5	7
Rotator cuff repair	2	3
Resection clavicular head	1	0
Arthroscopic procedures		
Stabilization	5	1
Acromioplasty	3	2
Rotator cuff repair	0	2
Debridement	4	10
Total	20	25

Table 2. Onset of Motor Block After Interscalene Block

	Minutes until loss of movement against gravity		
	Elevation of arm at the shoulder	Flexion of forearm at the elbow	*P* value
Proximal paresthesia	4.4 (±2.8) (range 2–10)	7.6 (±5.1) (range 2–16)	$P < 0.002$
Distal paresthesia	3.8 (±2.0) (range 2–8)	6.5 (±4.1) (range 2–16)	$P < 0.001$
	NS	NS	

NS, not significant.
Values are mean (±SD); paired *t*-test.

Patients received no sedation until completion of all measurements. Statistical analysis of data was done by analysis of variance, Scheffé F test, and paired or unpaired *t*-tests where appropriate.

Results

Forty-five interscalene blocks were performed. The first elicited paresthesia was observed to be proximal in 20 patients (45%) and distal in 25 patients (55%). There were no significant differences in age, height, weight, or gender between the proximal and distal paresthesia groups. After interscalene block, each patient developed adequate surgical anesthesia, and in no case was the block repeated or general anesthesia induced. The types of surgical procedures performed were similar in both groups (Table 1).

All 45 patients demonstrated complete loss of ability to elevate the upper arm at the shoulder (grade 0 motor ability) by 10 min after the block was administered. The mean time to achieve this degree of motor block was not different between the proximal and distal paresthesia groups ($P > 0.05$) (Table 2). Assessment of motor block at the elbow revealed that 44 of 45 patients had complete loss of ability to flex the forearm at the elbow against gravity by the end of the measurement period. The mean time to achieve this degree of motor block at the elbow was not different between the proximal and distal paresthesia groups ($P > 0.05$) (Table 2). The single patient who failed to achieve a complete motor block at the elbow by 16 min was in the proximal paresthesia group. By 2 min after the interscalene injection, this patient had a complete motor block at the shoulder and only grade 1 motor ability at the elbow; however, he retained weak antigravity motion at the elbow at the end of the measurement period. In both the proximal and distal paresthesia groups, motor block (grade 0 motor ability) at the shoulder significantly preceded motor block at the elbow (Table 2).

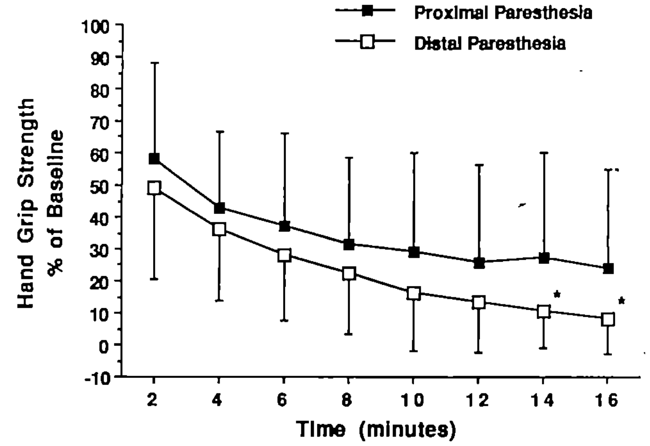

Figure 1. The decline in handgrip strength after interscalene block. Both proximal and distal paresthesia groups demonstrated decreases in handgrip strength by 2 min after block ($P = 0.001$), which continued to significantly decline through the measurement period ($P = 0.0001$; analysis of variance for two-factor repeated measures). Proximal and distal paresthesia groups had similar decreases in handgrip except at 14 and 16 min after block, when the distal paresthesia group demonstrated a significantly greater decrement in handgrip ($P = 0.03$; Scheffé F test). *$P < 0.02$ vs proximal paresthesia.

Handgrip strength was reliably reduced by 2 min after interscalene injection among all patients ($P = 0.0001$). The proximal and distal paresthesia groups showed similar reductions in handgrip strength throughout the measurement period except at 14 and 16 min after the injection, when the distal paresthesia group showed a significantly weaker handgrip than the proximal group ($P = 0.03$) (Figure 1).

Discussion

The most significant finding in our study is that each interscalene block performed after the elicitation of a shoulder paresthesia resulted in profound brachial plexus anesthesia. The explanation most commonly cited as to why shoulder paresthesias are unacceptable is that such a proximal paresthesia could theoretically result from needle stimulation of the suprascapular nerve after it has exited the fascial sheath that envelops the brachial plexus (4). If this occurs, any local anesthetic deposited would be expected to result in a selective block of the suprascapular nerve. Because the suprascapular nerve has no cutaneous innervation and provides motor innervation only to the supraspinous and infraspinous muscles, such a block would be easily discernible from a brachial plexus block. In the present study, when shoulder paresthesias were accepted such a selective blockade of the suprascapular nerve was never observed to occur.

The observation that 45% of initial paresthesias were to the shoulder underscores the clinical relevance of evaluating the reliability of proximal paresthesias when interscalene blocks are performed. Because we looked solely at the initial elicited paresthesia, a necessary conclusion is that in our study, almost half of the interscalene blocks were successfully completed more quickly because we accepted a shoulder paresthesia rather than continuing to pursue a more distal paresthesia. In addition, because multiple needle insertions may possibly result in nerve trauma, one may speculate that by accepting a proximal paresthesia and avoiding prolonged needle probing, the patient may be exposed to a reduced risk of postinjection nerve damage.

For this study, mepivacaine was used for interscalene blocks, because we have found this local anesthetic provides adequate duration of anesthesia for most shoulder procedures as well as rapid return of function after surgery. Because much of our shoulder surgery is performed on an ambulatory basis, this allows for early postoperative assessment of nerve function as well as determination of adequacy of pain relief before discharge. Although the dose of mepivacaine used was relatively large (10 mg/kg), we have found this to be a safe and effective dose for brachial plexus blocks, as have other authors (6).

In this study, we assessed brachial plexus block by evaluating the onset of motor rather than sensory blockade to allow us to use an objective measure of neural blockade (the dynamometer). In addition, because motor blockade often precedes sensory blockade (7), monitoring motor function allowed rapid completion of our measurements so as to minimize delay in preparation of patients for surgery. The observed sequential onset of motor blockade from proximal to more distal musculature has been described previously (8). The fact that there was little difference in the time-course of motor blockade between the proximal and distal paresthesia groups is compatible with the concept that in both situations, local anesthetic was deposited within the fascial sheath at approximately the same level (C-6). The slight difference in measured handgrip strength between the proximal and distal paresthesia groups near the end of the measurement period is not easily explained. It is possible that a more profound distal block results after a distal paresthesia and that this could have clinical implications when interscalene blocks are performed for more distal surgical procedures.

In summary, it was observed that during the performance of interscalene brachial plexus blocks, almost half of the initial elicited paresthesias were toward the shoulder and that in all cases, use of these proximal paresthesias resulted in brachial plexus anesthesia, which was satisfactory for shoulder surgery. We therefore recommend that paresthesias toward the shoulder be accepted in the performance of interscalene blocks for surgical procedures involving the shoulder.

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Influence of Volume on the Spread of Local Anesthetic-Methylene Blue Solution After Injection for Intercostal Block

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The purpose of this study was to evaluate the influence of the volume of methylene blue-local anesthetic on the spread of the injectate along the costal pleura. Twenty patients undergoing elective thoracotomy were studied. Twelve patients received intercostal nerve injection with 10 mL of 0.5% bupivacaine with methylene blue (10-mL group), and eight patients received 5 mL of 0.5% bupivacaine with methylene blue (5-mL group). The area of spread of the methylene blue was measured after the pleural cavity was incised. The 10-mL group had a mean area of spread of 51.1 cm^2 as opposed to 17.6 cm^2 for the 5-mL group ($P < 0.05$). In the 10-mL group, eight patients had bupivacaine-methylene blue spread to two intercostal spaces, three patients to three intercostal spaces, and one patient to four intercostal spaces. In the 5-mL group, seven patients had bupivacaine methylene blue spread confined to one intercostal space and one patient to two intercostal spaces. We conclude that a potential anatomic space exists between the costal pleura and the internal intercostal muscle and that the spread of local anesthetic after intercostal nerve block injection is volume dependent.

(Anesth Analg 1992;75:389–91)

Intercostal nerve block with local anesthetic solutions is indicated for reducing pain after thoracotomy and upper abdominal surgery, after rib fracture, and in the treatment of intercostal neuralgia. The block can be achieved by a single injection, multiple injections, and continuous catheter techniques; however, there is controversy with regard to the effect of the technique on spread of the solution. The spread of local anesthetic after intercostal nerve block has been studied in both patients and cadavers (1,2). Although there has been a suggestion that volume may affect the spread of local anesthetic, the comparative volumes have been small (3 and 5 mL) (1,2). There is also the possibility that because of autolysis, spread in the cadaver may be greater than in the patient (3). Spread of local anesthetic cephalad and caudad from the injection site would suggest that a potential anatomic space exists between the costal (parietal) pleura and internal intercostal muscles. This potential space is not identified as such in standard anatomy textbooks (4). A number of recent studies in anatomic specimens and volunteers demonstrated that the spread of the injected solution is confined to one intercostal space (5) or to multiple spaces (6,7). These differences could be related to whether the needle tip is superficial or deep to the internal intercostal muscle. In the present study we sought to evaluate, in live subjects, the relationship between two volumes (5 and 10 mL) of injectate and the spread of local anesthetic mixed with methylene blue after intercostal nerve block. This study attempted to answer two questions. First, can multiple intercostal nerve blocks be achieved with a single injection? Second, does a potential anatomic space exist between the costal pleura and the intercostal muscles?

Methods

After approval by the Indiana University Committee for Protection of Human Subjects and informed patient consent, 20 patients undergoing elective thoracotomy were studied. All patients received general anesthesia consisting of thiopental (4 mg/kg IV) for induction, either vecuronium (0.1 mg/kg IV) or succinylcholine (1.5 mg/kg IV), tracheal intubation, and inhaled isoflurane and nitrous oxide in oxygen. After the initiation of anesthesia, each patient was positioned in the appropriate lateral decubitus position for thoracotomy. Before the surgical incision, 0.5% bupivacaine with methylene blue was injected into the intercostal space two interspaces caudad to the proposed surgical incision. Eight patients received

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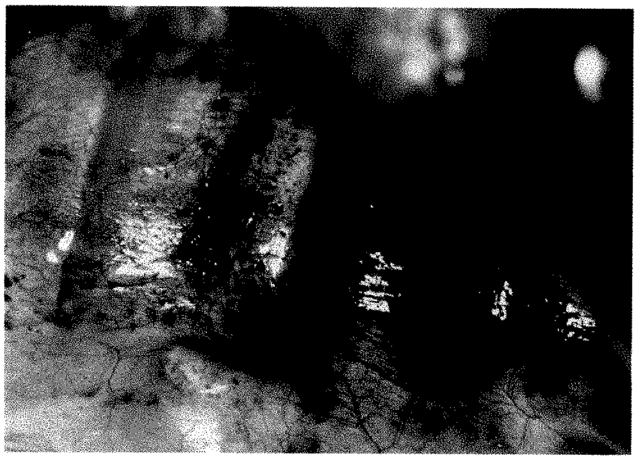

Figure 1. Photograph of the costal pleura demonstrating spread of methylene blue across three intercostal spaces after a single intercostal injection with 10 mL of 0.5% bupivacaine with methylene blue. Injection of the solution was performed at the angle of the rib, near the central part of the coloration. The spread of methylene blue was in all directions.

5 mL of bupivacaine with methylene blue, and 12 patients received 10 mL of bupivacaine with methylene blue. The intercostal injection was performed with a 2-in. 22-gauge needle at the posterior angle of the rib 8 cm from the dorsal midline. The needle was directed 45° in the cephalad direction. After the inferior margin of the rib was contacted, the needle was advanced 3 mm beyond the rib. At that point, the needle was fixed and the bupivacaine-methylene blue solution injected. After the intercostal injection, the surgery was begun. After the pleural cavity was exposed, the surgeon (unaware of the volume of injectate) measured the length and width of the spread of the methylene blue. The time from injection to measurement of the area of spread was approximately 30 min. The area of the spread was calculated from the length and width of the stained area. The number of intercostal spaces discolored were counted. Statistical comparisons of the area of spread and the number of intercostal spaces traversed were performed. Statistical analysis used the Wilcoxon signed rank test and two-sample *t*-test. A *P* value <0.05 was considered significant.

Results

Seven of the eight patients who received 5 mL of bupivacaine-methylene blue had the injectate confined to one intercostal space. Of the 12 patients receiving 10 mL of bupivacaine-methylene blue, eight had spread to two intercostal spaces, three had spread to three intercostal spaces (Figure 1), and one had spread to four intercostal spaces. The patients receiving 10 mL had a mean area of spread of 51.1 ± 19 (SD) cm^2 as opposed to 17.6 ± 7.6 cm^2 ($P < 0.05$) (Table 1). There was no evidence of a preferential medial spread to the paravertebral region. The solution spread medially, laterally, superiorly, and inferiorly from the point of injection.

Table 1. Spread of Local Anesthetic After Intercostal Nerve Block and Area of Staining of Costal Pleura With Methylene Blue

	10-mL Injectate (n = 12)	5-mL Injectate (n = 8)
Width (cm)	6.0 ± 1.5	2.2 ± 1.7
Length (cm)	8.7 ± 1.6	6.9 ± 2.3
Area (cm^2)	51.1 ± 19	17.6 ± 7.6[a]
No. of intercostal spaces	2.4 ± 0.06	1.1 ± 0.03[b]

10 mL Injectate, 10 mL of 0.5% bupivacaine with methylene blue; 5-mL Injectate, 5 mL of 0.5% bupivacaine with methylene blue.
Values are mean ± SD.
[a] $P < 0.05$.
[b] $P < 0.02$.

Discussion

This study demonstrates that the spread of local anesthetic-methylene blue after intercostal injection is volume dependent. In general, a volume of 5 mL is confined to one intercostal space, whereas 10 mL will spread to multiple intercostal spaces.

Other studies have demonstrated some cephalad-caudad spread, but those studies used smaller volumes injected into cadavers. Nunn and Slavin (1) injected 3 mL of India ink into anatomic cadaver preparations and found spread cephalad and caudad involving the intercostal space above and below the injection space. Moore (2) also demonstrated lateral and medial spread after intercostal injection of India ink into cadavers. Moore did not observe cephalad or caudad spread of the dye in most of the specimens. This difference between the studies of Nunn and Slavin (1) and Moore (2) might be explained by size of the needle bevel. A longer bevel is associated with spread of the injectate into more fascial planes. The use of cadavers also introduces the possibility of artificial tissue planes produced by tissue autolysis after death.

In a study of live subjects, Moore et al. (3) injected 5 mL of radiographic dye into the intercostal space and observed spread in all four directions. Mowbray and Wong (8) injected 3 mL of bupivacaine with methylene blue into both patients and cadavers. The solution was confined to one intercostal space in 86% of the patients and 84% of the cadavers. Some of the patients in the Mowbray and Wong study did, however, demonstrate spread to more than one intercostal space. In these studies the actual degree of neural blockade was not specifically discussed. Studies injecting radiopaque dye with the local anesthetic demonstrated localization to one intercostal space in some patients and spread to multiple intercostal spaces in other patients (6,7). The spread of the dye-local anesthetic solution in our study resembles the spread demonstrated by Crossley and Hosie (6) in a radiologic study. The use of 10 mL of solution in our study produced spread in all directions. There was no preferential medial spread.

Our study demonstrates conclusively that the spread of local anesthetic after intercostal nerve block is volume dependent. Spread in the space between the costal (parietal) pleura and the intercostal muscles depends on proper placement of the needle. The needle should be advanced 3 mm beyond the inferior rib margin to ensure proper deposition of the local anesthetic to facilitate spread. If the needle is too shallow, then the local anesthetic will be confined to one intercostal space. Although our study addresses intercostal spread, the extent of local anesthesia produced was not measured.

Our finding is of clinical significance, because multiple intercostal nerves can possibly be blocked with one injection. This technique can therefore be useful in postoperative analgesia. We have not studied this technique in patients who have a disruption in the parietal pleura (e.g., neoplasm). It is conceivable that in patients with a disrupted pleura, spread of the local anesthetic solution will be restricted. Further clinical studies are warranted in a variety of different clinical situations. A clinical study correlating the degree of intercostal spread with analgesia is also justified. Johnson et al. (9) demonstrated multiple segmental intercostal nerve block by using a continuous catheter technique in the paravertebral region; however, our study addresses the issue when the local anesthetic solution is injected with the conventional single injection technique. The complications associated with intercostal nerve block, such as toxic reactions from rapid absorption of local anesthetics and epinephrine, pneumothorax, and hypotension secondary to paravertebral sympathetic blockade, can occur with any technique. However, a larger volume single injection is not associated with more rapid absorption than multiple injections as long as the total local anesthetic dose is not excessive.

In summary, we have demonstrated that a potential anatomic space does exist between the costal pleura and the internal intercostal muscle and that a local anesthetic-methylene blue solution will spread to multiple intercostal segments. This finding suggests the possibility of achieving multiple intercostal nerve blocks with a single injection of 10 mL of local anesthetic, thereby decreasing the incidence of, or avoiding complications associated with, multiple intercostal injections. Further work in volunteers with this technique is required to determine the number of dermatomes anesthetized.

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Repeated Intrathecal Injections of Dezocine Produce Antinociception Without Evidence for Neurotoxicity in the Rat: A Study of Morphometric Evaluation of Spinal Cord Histology

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This study was designed to determine the antinociceptive and spinal cord histologic effects of a new agonist/antagonist opioid drug dezocine. This drug was injected intrathecally in rats at a dose of 50 or 125 μg twice daily for 14 days. The tail-flick test showed that the antinociceptive effect declined gradually, with no detectable effects by day 14. Quantitative histologic techniques and light and electron microscopy showed that neither dose, compared with vehicle, created any morphologic changes in the spinal cord that could be attributed to a neurotoxic or otherwise degenerative effect of the drug. In conclusion, dezocine is a drug that gives rise to sustained antinociceptive effects when administered intrathecally and causes no morphologic changes in the rat spinal cord that could be indicative of neurotoxic potential.

(Anesth Analg 1992;75:392–9)

Intrathecal or epidural administration of opioid analgesic drugs has become increasingly used for treating patients with pain. The analgesia is produced by activation of opioid receptors located in the dorsal portion of the spinal cord (1). When injected intrathecally, morphine inhibits release of primary afferent substance P (2) and also hyperpolarizes the secondary dorsal horn neuron (3) receiving the nociceptive afferent. With repeated injections of morphine, the antinociceptive effect declines both clinically (4) and experimentally in animal models of nociception (5).

Dezocine is a new analgesic drug, recently introduced clinically for systemic administration. Its profile is that of a mixed opioid agonist/antagonist, with antinociceptive effects found in animals after systemic injection (6). This class of opioids may potentially have advantages over traditional full agonist opioids, with slower development of tolerance and possibly a lesser extent of supraspinally mediated respiratory depression. This profile may warrant spinal cord administration of dezocine. Recently, however, dezocine was reported to have deleterious effects in the spinal cord in dogs after repeated administration (7). However, the investigational procedure used by those authors gave rise to profound morphologic changes in both control and dezocine-treated animals, suggesting that the model may not be well suited for such studies.

The aim of the present investigation was to study the effects on nociceptive behavior in animals after intrathecal administration of dezocine, both after short-term and repeated dosing, and to ascertain the morphology of the spinal cord after such treatment.

Methods

After approval by the regional animal ethics committee, male Sprague-Dawley rats (Alab, Sollentuna, Sweden), weighing 320–350 g, were kept in animal rooms thermostatically maintained at 21 ± 1°C and a regulated dark-light environment (lights on at 6 AM and off at 6 PM). The rats were housed on sawdust bedding material in groups of five for at least 5 days before surgery. After the surgery and until termination of the experiment, the rats were housed in individual cages. They had free access to standard

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food pellets and tap water throughout the experiment.

Three milliliters per kilogram of an aqueous solution containing (per 100 g) chloral hydrate, 4.25 g; ethanol, 9 g; propylene glycol, 42.8 g; sodium pentobarbital, 0.98 g; and magnesium sulfate, 2.1 g (Apoteksbolaget, Stockholm, Sweden) was administered intraperitoneally to anesthetize the animals. The doses of dezocine HCl (Astra Pain Control AB, Södertälje, Sweden) were calculated as salt.

Preparatory surgery for intrathecal injections was performed during equithesine anesthesia. A polyethylene catheter (PE-10, Clay Adams), previously streched to double length, was inserted into the spinal subarachnoid space through a slit in the atlantooccipital membrane (8). The length of the catheter (8.5 cm) was chosen to place the catheter tip at the L-1 region of the lumbar enlargement. Only rats demonstrating normal motor behavior by a global assessment after surgery were included in this study.

Tail-flick testing (9) was performed with an IITC Inc. model 33 analgesimeter. During testing, a rheostat-controlled light beam was focused on the tip of the tail, and the time interval from the onset of the heat stimulus to the flick of the tail was recorded. A cutoff time of 15 s was used to avoid tissue destruction. Three days after surgery, the rats were habituated to a restraining tube used for tail-flick testing at three consecutive 10-min sessions. One week after surgery, the experiment was started. Each group contained seven to eight rats.

The drugs were administered dissolved in 10 μL of 0.9% saline solution, followed by 15 μL of 0.9% saline solution to flush out the catheter. After the injections, a 0.26-mm-diameter plastic plunger was inserted into the PE-10 catheter as a stopper. Dezocine HCl (50 or 125 μg) or 0.9% saline solution was administered through the intrathecal catheters at 8 AM and 4 PM each day for 14 days. The smaller dose was chosen to ascertain complete analgesia. To determine any possible neurotoxic effect, the strongest concentration that could be made (12.5 mg/mL) was also tested. Tail-flick testing was performed each day before (predrug latency) and 30 min after the 8 AM intrathecal injection.

Twenty-four hours after the last intrathecal injection of saline solution or dezocine, the rats were reanesthetized with the same drug and killed by transcardial perfusion with 200 ml of Tyrode's solution (38°C, pH 7.4) containing 10,000 E heparin per liter followed by a 500-mL mixture of 2% glutaraldehyde and 1% formaldehyde in 0.1 M phosphate buffer (38°C, pH 7.4). The perfusion was continued for approximately 20 min (10). The spinal cord was removed together with the catheter after bilateral laminectomy of the spine.

Under a dissection microscope, the L-1 segment was excised. It was stored for 12 h in cold fixative (4°C). Only animals with the tip of the catheter at the level of the L-1 segment verified under the microscope were included in the study. The L-1 segment was rinsed in the buffer and then serially sectioned by means of a vibratome. Thereafter, the vibratome sections were rinsed in a 0.1 M sodium cacodylate buffer (pH 7.4), postfixed for 30 min in 2% OsO_4 dissolved in cacodylate buffer, and dehydrated in graded ethanol and embedded in a epoxy resin (Agar 100) between Teflon-sprayed slides and 100-μm-thick acetate foils (11). After the sections were examined with the light microscope, five random tissue blocks containing the dorsal horn of the spinal cord were excised from each animal and reembedded for fine sectioning (2 μm). For electron microscopy, ultrafine sections (500 Å) were made from both the ventral and dorsal horns. The fine sections were stained with toluidine blue and the ultrathin sections with uranyl and lead citrate.

The fine sections were used for quantitative analysis of the dorsal horn morphology (12–14). The variation in total cell number (per mm^3), dark cell number (interpreted as inflammatory cells) in laminas I–III of each section, mean cell volume (μm^3), and cell ratio (%) in a reference volume of the dorsal horn were used as sensitive variables of spinal neurotoxicity. The reference volume contained laminas I–III of a rostrocaudal column throughout the whole L-1 segment. It was measured in each animal according to the Cavalieri principle (15). With the light microscope, the outlines of the transverse area of the reference volume were drawn with the aid of a drawing tube attached to the microscope. By means of a graphic pen-data tablet device (MOP, Kontron), that area was measured. The sections used were spaced through the L-1 segment with an intervening distance of at most 0.1 mm. We found the length of the L-1 segment by serial planimetry of the total number of the L-1 sections to constitute approximately 3.1% of the total length of the spinal cord. Thus, the length of the spinal cord was measured in each animal, and the length of the L-1 segment was calculated.

The number of cells within the reference volume (V_{ref}) was calculated according to the disector principle (16). A disector (V_{dis}) is a small tissue block in the reference volume. On a section, the outlines of the area of the disector were drawn with the drawing tube. In that area the cell nucleoli of the neurons were sampled, and the cells were drawn. This particular area was then sought on the next serial section and the cell nucleoli of the drawn cells not sectioned by this "sought" section were counted (Q). Within each animal, 30 disectors, all the same size, were sampled

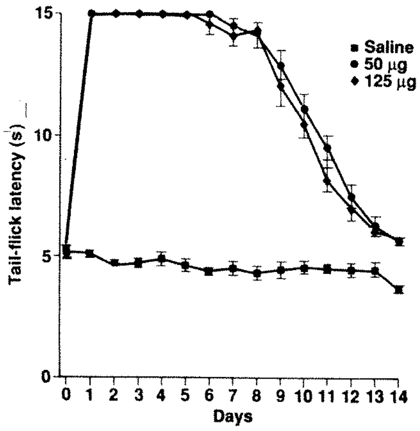

Figure 1. Antinociceptive effects measured in the tail-flick test of dezocine (50 or 125 μg) and saline solution after twice-daily intrathecal administration. Tail-flick latencies were measured each day after the first daily dose. The cutoff time was 15 s. Results are expressed as mean ± SEM ($n = 7$).

from the reference volume. The coefficient of error was estimated by splitting this sample into two groups (12). A coefficient of error <0.05 was statistically accepted for the sample frame.

A systematic random sample of sections was analyzed in each animal, and the number of cells (N) in the reference volume was calculated according to the formula $N = \Sigma\, Q\cdot V_{ref}\cdot V_{dis}^{-1}$. The mean cell volume was calculated from the total cell volume and total cell number within the reference volume. The total cell volume was estimated by point-counting as the ratio between the area of the cell bodies and the area of the disectors (17). The cell number (N) was then normalized to cell number per cubic millimeter for comparison among the animals. The values for total cell number, the number of dark cells, mean cell volume, and cell ratio were compared with control values. Student's *t*-test was used to test for significant differences, and a probability of <0.05 was accepted as statistically significant.

The neuronal tissue of the L-1 segment was examined with the electron microscope for signs of toxicity with respect to karyolyses, edema, and the general appearance of the mitochondria, microtubules, neurofilaments, and synaptic vesicles. The preservation of the tissue as well as the myelin damage was also studied. Occasional splits of the myelin sheets were accepted because this can also be seen in untreated neuronal tissue.

Results

Intrathecal administration of 50 μg of dezocine (Figure 1) in rats induced an antinociceptive effect in the tail-flick test that reached the 15-s cutoff value 30 min after the first injection. No signs of tolerance were seen until after approximately 1 wk of twice daily injections, when the antinociceptive effect started to diminish. Even at the termination of the experiment, there was still some antinociceptive effect seen in the dezocine-treated rats compared with the saline solution-treated animals. When 125 μg of dezocine was administered twice daily, the antinociceptive effect and tolerance development were similar, as with the smaller dose. Intrathecal administration of 0.9% saline solution did not induce any antinociceptive effect during the experiment, but there was a minor decrease in the tail-flick latency after 14 days of treatment.

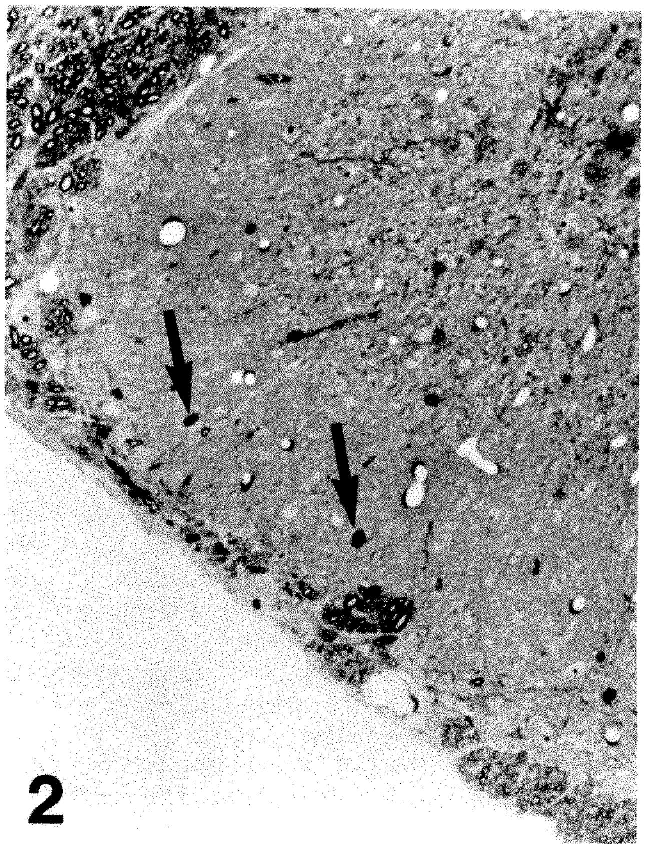

Figure 2. Light micrograph of a toluidine-stained plastic-embedded section from lumbar spinal cord (L-1 segment) after intrathecal injection of saline solution for 14 days. Normal findings (rat S2 [Table 1]). Note the presence of dark inflammatory cells (*arrows*). ×450.

No effect on general behavior, such as an effect on the motor system or weight loss, was noticed after the smaller dose. After the larger dose, some activation of locomotion was seen as well as rearing, grooming, and jumping.

In three of the rats, a mild inflammatory reaction was seen along the course of the catheter. In that area, dark cells were frequently observed. These cells

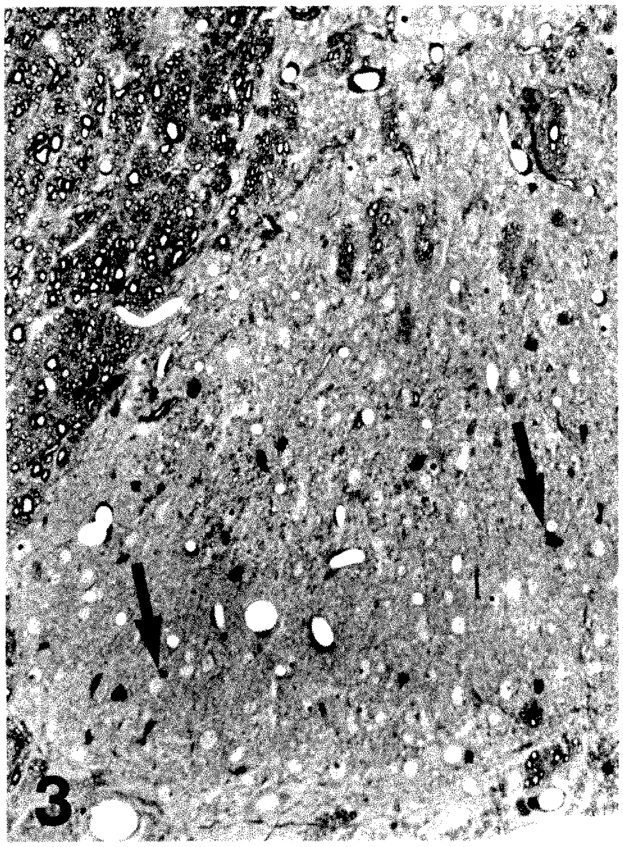

Figure 3. Light micrograph of the dorsal horn and parts of the intermediate substance (L-1 segment) demonstrating normal morphology 14 days after intrathecal administration of 125 μg of dezocine (rat D2 [Table 1]). In the dorsal horn, dark inflammatory cells (*arrows*) are seen. Stained with toluidine blue. ×480.

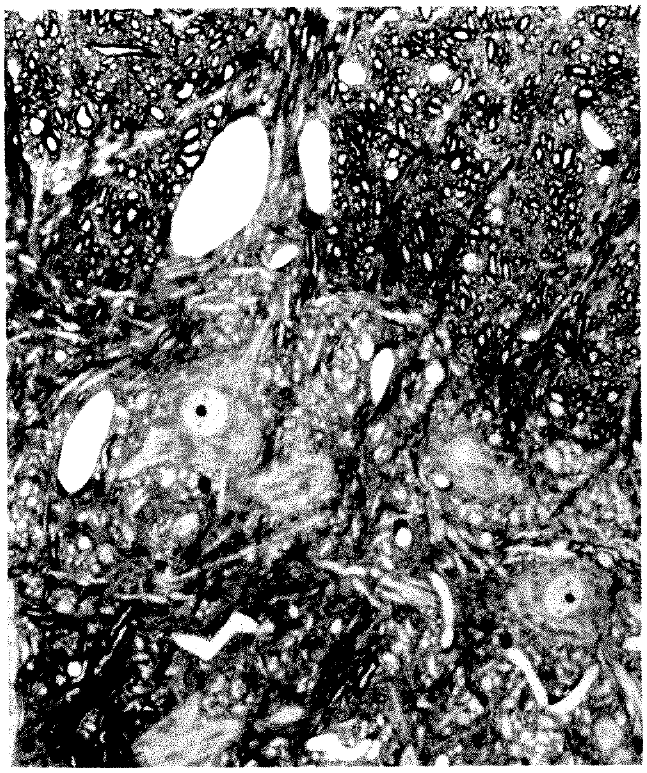

Figure 4. High-power light micrograph of the ventral horn (rat D5, intrathecal dezocine, 50 μg [Table 1]) showing two normal motor neurons and spinal tracts. Stained with toluidine blue. ×650.

were interpreted as the inflammatory cells. No significant differences were noticed between the rats injected with dezocine and the untreated control rats with respect to tissue reaction. Thus, dark inflammatory cells could occasionally be observed in the gray matter of both groups (Figures 2 and 3). They were scattered throughout the ventral and dorsal horn. The neurons of the dorsal horn and the ventral motor neurons (Figure 4) had the same appearance in the dezocine-injected rats as was observed in the control rats. The spinal tracts demonstrated no visible signs of injury or spongy appearance of the myelin sheets.

Quantitative Investigations

The calculations of the reference volume revealed no statistically significant differences between the control animals (0.75 ± 0.034 mm^3) (mean ± SEM) and the rats injected with 50 μg of dezocine (0.69 ± 0.037 mm^3) or 125 μg of dezocine (0.68 ± 0.035 mm^3). In all of the rats, the reference volume ranged between 0.52 and 0.89 mm^3. The total number of cells per cubic millimeter in laminas I–III of the dorsal horn, as well as the number of dark (inflammatory) cells, demonstrated no significant differences between the control and the dezocine-injected animals. The individual values (means ± SEM) are shown in Table 1. Furthermore, the ratio of neuronal cell bodies in the reference volume was 5.2% (mean) for the saline solution-injected rats, which was slightly higher than the mean value of 5.0% for the rats injected with dezocine. This difference, however, was not statistically significant.

The calculations of the mean cell volume from the values of total cell volume in the reference volume and the total number of cells revealed no statistical differences between the saline solution- and the dezocine-injected rats. Likewise, the mean cell volume reached a higher value in the control (620 ± 20 μm^3) (mean ± SEM) than in the dezocine-injected animals. The corresponding values for these two groups were 610 ± 20 and 580 ± 20 μm^3, respectively (mean ± SEM). The coefficient of error demonstrated $P < 0.05$ for both the control and the dezocine-injected animals.

Table 1. Individual and Mean ± SEM Values for Total Cell Number, Dark Cell Number, Mean Cell Volume, and Cell Ratio in Laminas I–III of the Dorsal Horn in Rats Intrathecally Injected With Saline Solution and Dezocine

Rat No.	Total cells (No./mm^3)	Dark cells (No./mm^2)	Mean cell volume (μm^{-3})	Cell ratio (%)
Saline solution				
S1	92,000	121	570	5.2
S2	83,000	95	590	4.8
S3	91,000	255	520	4.7
S4	82,000	182	690	5.6
S5	79,000	114	660	5.2
S6	80,000	141	680	5.4
S7	84,000	136	630	5.3
S8	87,000	141	560	4.9
Mean				
±SEM	85,000	148	620	5.2
	±1700	±20	±20	±0.1
Dezocine (50 μg)				
D1	79,000	150	620	4.9
D2	85,000	206	550	4.7
D3	83,000	152	610	5.1
D4	87,000	157	530	4.6
D5	84,000	164	600	5.0
D6	91,000	133	570	5.2
D7	82,000	211	680	5.6
D8	102,000	117	470	4.8
Mean				
±SEM	87,000	160	580	5.0
	±2500	±10	±20	±0.1
Dezocine (125 μg)				
D1	79,000	180	600	4.7
D2	95,000	164	520	4.9
D3	88,000	67	570	5.0
D4	80,000	108	600	4.8
D5	74,000	100	710	5.3
D6	84,000	133	550	4.6
D7	71,000	88	710	5.1
D8	91,000	147	590	5.4
Mean				
±SEM	83,000	120	610	5.0
	±2900	±10	±20	±0.1

Electron Microscopic Observation

With the electron microscope, no morphologic differences could be detected between the saline solution- and dezocine-injected animals. The cell bodies of the neurons demonstrated normal shapes (Figure 5). Their cell membranes were intact, and the nuclei were seen in the typical central position with a distinct nucleoli. The organelles of the neurons were normal in appearance as well. Furthermore, the microtubuli, neurofilaments, and mitocondria of the axons displayed normal morphology. The boutons contained small, round vesicles.

The dark cells observed with the light microscope of both saline solution- and dezocine-injected rats were identified as microglial cells with prominent perikarya (Figure 6). They were scattered throughout the neuropil of the dorsal and ventral horns. Adjacent to the microglial cells, no degenerating cell bodies, axons, or boutons were found. Neither could phagocytosed cells be seen in the gray matter.

The perivascular cells and perivascular astrocytes also demonstrated normal morphology. Occasionally, the perivascular astrocytes contained round and sometimes even irregularly shaped dense granules (Figure 7). The myelin sheets sometimes showed concentric splits but without any visible differences between the control and dezocine-injected animals. Finally, preservation of the tissue was generally good.

Discussion

The present investigation demonstrates that dezocine is a drug that exerts antinociceptive effects when administered intrathecally to rats and that tolerance develops at a considerably slower rate than has been reported in the literature for morphine (5). We have also found that the spinal cord when examined postmortem shows no signs of neurodegenerative or other effects indicating that dezocine may be toxic.

The method used (i.e., a combination of light and electron microscopic observations with a quantitative morphometric method) has increased the sensitivity of investigations of neurotoxicology (14). After repeated injections of substance P, guanfacine, and somatostatin, light microscopic observations revealed toxic reactions of the nervous tissue (18–20). Interpretation of these limited data is difficult because the identity of the cells affected cannot be determined, especially with respect to the occurrence of microglial cells.

In the present study, there were no significant differences between the number of cells per cubic millimeter in the dorsal horn of the control rats (85,000) and those rats injected with either 50 μg (87,000) or 125 μg (83,000) of dezocine. These values are in accordance with the mean number of cells found in nonsurgical rats (14). The presence of a small number of the microglial cells in both the saline solution- and dezocine-injected rats was interpreted as a normal phenomenon in neuronal tissue. Another explanation for the occurrence of the microglial cells may be the tissue preparation; however, this seems unlikely, because the electron microscopic analysis demonstrated well-preserved tissue. In electron microscopic studies of normal nerve tissue, microglial cells have been found in small numbers with typical morphology (21,22). After lesioned axons, they ap-

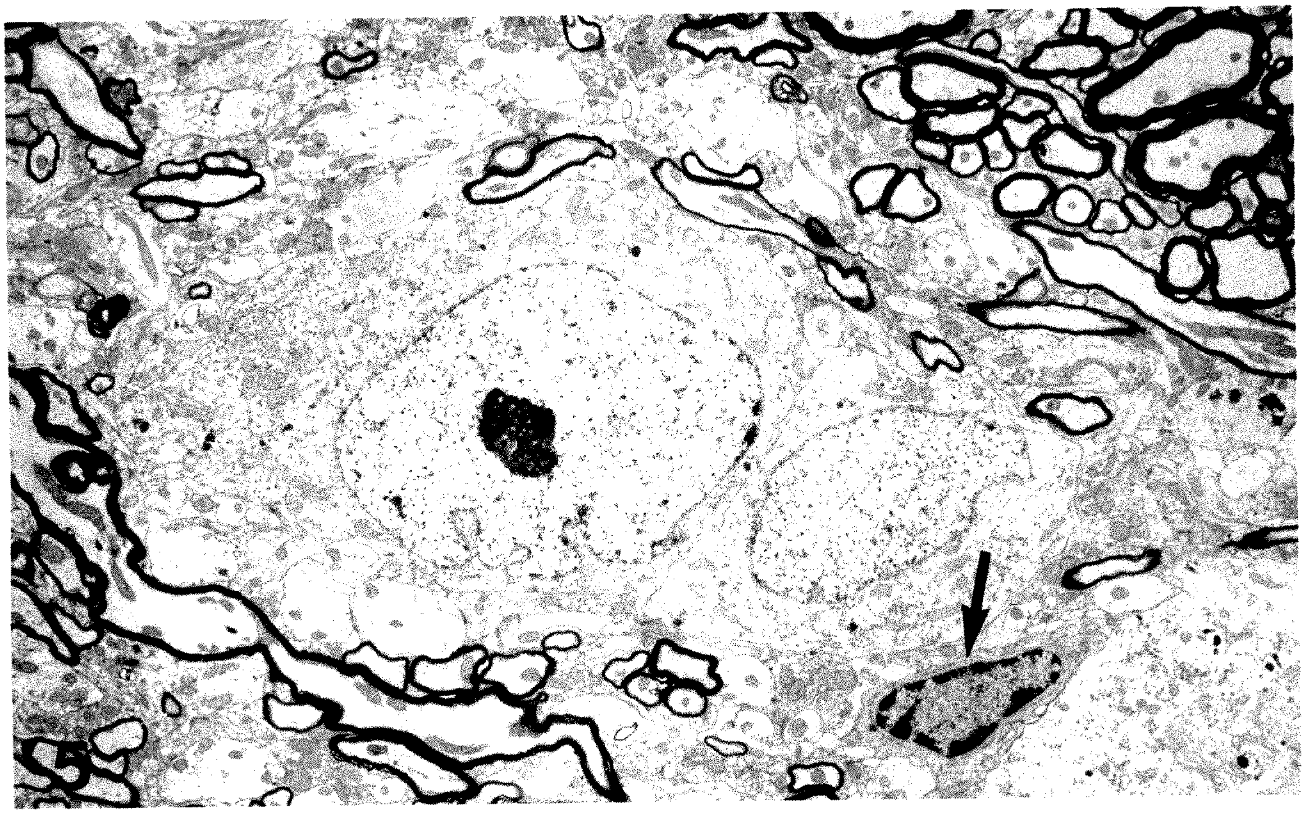

Figure 5. Electron micrograph of two normal neurons and a small astrocyte (*arrow*) in lamina II of the dorsal horn (rat D1, intrathecal dezocine, 125 μg [Table 1]). ×15,000.

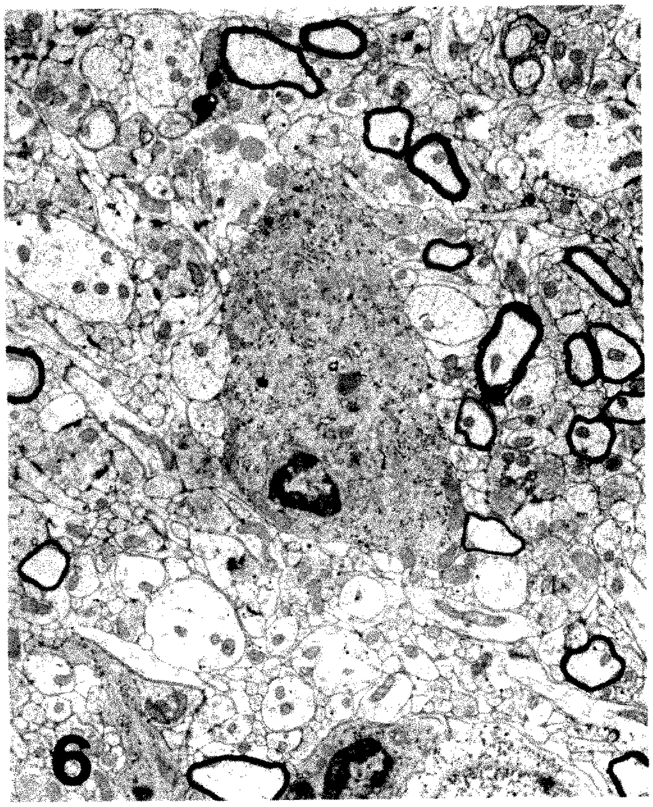

Figure 6. Electron micrograph of a microglial cell in lamina I of the rat shown in Figure 2. The inflammatory cell is surrounded by normal neuropil. ×10,500.

peared in increased numbers and were often located near degenerated structures (22).

The morphometric method, which uses the "disector principle," requires no assumptions about the shape of the investigated cells and is an unbiased stereologic estimator of total cell number and mean cell volume (12). The reference volume was measured in each animal (14) so that it was possible to estimate the total cell number and mean cell volume independently of tissue swelling or shrinking caused by the fixation, dehydration, or plastic embedding of the vibratome sections. Finally, the mean cell volume, which may be the most sensitive variable to detect minor neurotoxicologic reactions of the nerve cells (such as variation in cell volume), demonstrated no significant differences between the saline solution- and dezocine-injected animals. This is in accordance with the values found in normal rats transcardially perfused with the same mixture of glutaraldehyde and formaldehyde used in this study (14).

The L-1 segment most adjacent to the tip of the catheter, where the concentration of dezocine would be the highest after the injections, showed no degenerated or phagocytosed cells at the electron microscopic level. Such morphologic changes would have been an expected sign of neurotoxicity or neurode-

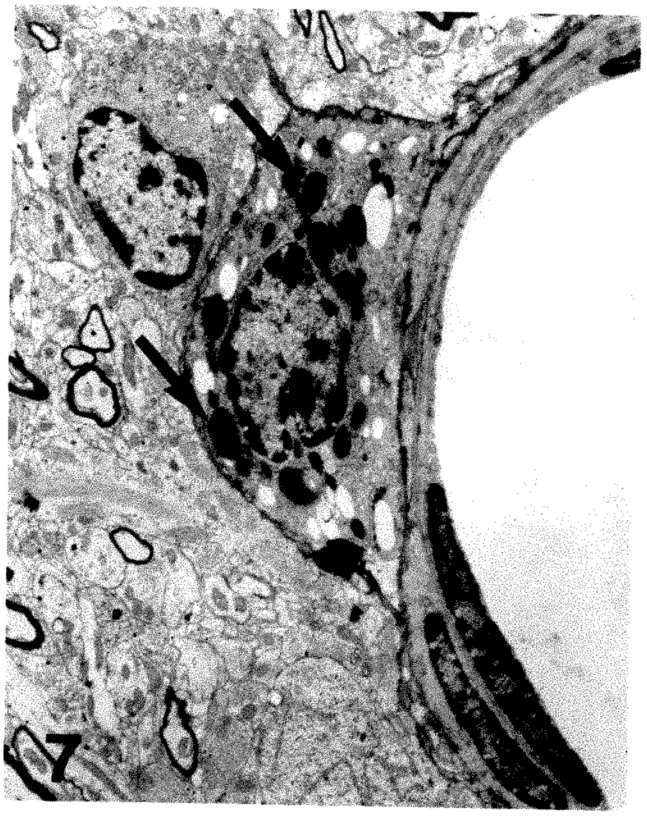

Figure 7. Electron micrograph of perivascular cells in the ventral horn (rat D8, intrathecal dezocine, 125 μg [Table 1]). The astrocyte contains oval, dark inclusions and vacuoles (*arrows*). The pericyte, as well as the neuropil adjacent to the vessel, shows normal morphology. ×24,500.

generation from other causes. The morphologic study was performed on the L-1 segment, because it was previously shown that this does not undergo any structural artifacts caused by injection (18,23). We previously found that the mild inflammatory reaction that may occur in close proximity to the catheter has no influence on morphology elsewhere in the spinal cord (14,23); however, Coombs and coworkers (7) found extensive fibrosis and inflammatory reactions after spinal administration of both saline solution and dezocine in dogs. The exact cause of the degeneration could not be established, but severe leptomeningeal reactions in both control and drug-injected animals seem to limit the value of repeated intrathecal injections in dog models for assessment of spinal drug toxicity.

In conclusion, repeated intrathecal administration of dezocine causes an antinociceptive effect that undergoes tolerance at repeated twice-daily injections; however, this tolerance develops more slowly than that previously reported for morphine (5). When injected twice daily over 14 days, dezocine produced no toxicologic effects in the rat spinal cord, as determined by quantitative analysis and light and electron microscopic observations. Dezocine may thus have clinical potential as a spinally administered drug for treatment of certain severe pain states.

We thank Kärstin Flink and Ingmarie Olsson for skillful technical assistance.

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Effects of Interpleural Bupivacaine (0.5%) on Canine Diaphragmatic Function

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Several authors have questioned the potential for phrenic nerve paralysis with interpleural analgesia. This study was designed to examine the potential for phrenic nerve paralysis with the use of interpleural bupivacaine in dogs. Seven dogs were anesthetized, tracheally intubated, and allowed to breathe spontaneously with halothane/oxygen while in the supine position. After a midline laparotomy, two wires were inserted into the costal portion of each hemidiaphragm for measurement of electromyographic (EMG) signals. A balloon catheter was placed in the abdominal cavity to measure abdominal pressure. The abdomen was then closed. Airway pressure was measured through a side port in the endotracheal tube. Bilateral interpleural catheters were inserted with the loss-of-resistance technique. Each dog was used for two experiments, one on each side, except for one animal. To assess the contribution of the ipsilateral diaphragm to total respiratory effort, the airway was occluded at functional residual capacity for three consecutive breaths, and EMG, airway pressure, and abdominal pressure were measured. In five of nine experiments with bupivacaine, there was complete loss of EMG activity on the side of the injection. In two dogs, there was partial loss of diaphragmatic function, and in the remaining two, there was no change in EMG. In the normal saline solution group ($n = 4$), there was no change in the EMG. Two dogs that received bilateral bupivacaine injections developed paradoxical respiration with negative inspiratory intraabdominal pressures. Phrenic nerve paralysis or paresis can occur with interpleural blockade. The factors affecting the occurrence of this complication remain to be elucidated.

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Interpleural administration of local anesthetics provides excellent postoperative analgesia for unilateral surgical procedures, such as cholecystectomy via a subcostal incision, mastectomy, or thoracotomy (1–5). Bilateral interpleural catheters have also been used to provide analgesia for major thoracoabdominal procedures (6). Initial reports concerning interpleural analgesia showed a beneficial effect on postoperative pulmonary function (2,4,7). More recent clinical studies have questioned this beneficial effect and have shown no improvement in postoperative forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1) despite improvement in postoperative pain scores (8,9). The reason for the lack of improvement in postoperative spirometry is not known, but one of the hypotheses is that phrenic nerve paralysis may occur with interpleural administration of local anesthetics (8,10,11).

The purpose of this study was to examine the effect of interpleural bupivacaine on diaphragmatic function and to determine whether diaphragmatic paralysis can occur with this technique.

Methods

Seven mongrel dogs, weighing between 15 and 25 kg, were studied. The animals were anesthetized with thiopental (10 mg/kg) and their tracheas intubated with a 9-mm internal diameter endotracheal tube. The dogs were allowed to breath spontaneously, and anesthesia was maintained with 1% halothane in oxygen, delivered via a calibrated Fluotec vaporizer. Femoral venous and arterial lines were inserted for administration of intravenous fluids and blood gas determinations. A midline laparotomy was performed, and two wires were inserted parallel to one another into the costal portion of each hemidiaphragm to measure diaphragmatic electromyographic activity (EMG). The wires used were Ethicon cardiac pacemaker wires, which have an uninsulated distal portion that was inserted into the muscle and

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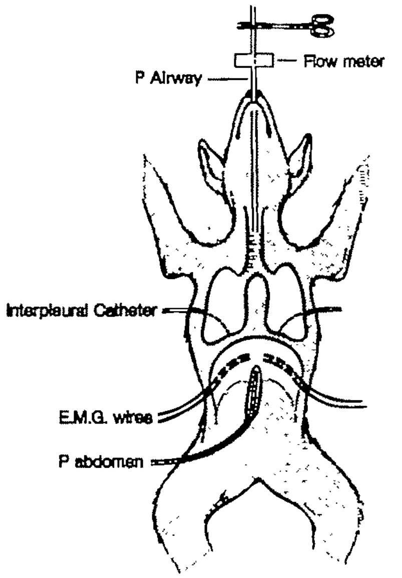

Figure 1. Experimental preparation. Note the bilateral interpleural catheters and electromyographic (E.M.G.) wires in each animal. P Airway, airway pressure; P abdomen, intraabdominal pressure.

an insulated portion that was passed out through the abdominal wall. A balloon catheter was placed in the abdomen for measurement of intraabdominal pressures. The catheter was made of polyethylene tubing and was 1.19 mm in internal diameter. The abdomen was closed in two layers. Bilateral interpleural catheters were then inserted in the posterior axillary line at either the seventh or eighth intercostal space. The technique used for insertion is similar to that described by Stromskag et al. (1). Portex epidural catheters were inserted into the pleural space to a depth of 10 cm at the skin and sutured in place.

Airway pressure was measured through a side port in the endotracheal tube. Both airway pressure and intraabdominal pressure were measured with a Validyne MP45-14 differential pressure transducer. One milliliter of air was injected into the abdominal balloon catheter. The diaphragmatic wires were attached to a Grass high-impedance probe (model HIP511, Grass Instruments Co., Quincy, Mass.) and a ground wire was attached to subcutaneous tissue at the site of the femoral incision. The signals were then amplified, rectified, and averaged with a moving time averager with a 100% response time of 100 ms. Both raw and averaged EMG signals were recorded. The EMG activity of each hemidiaphragm was measured, but only one hemidiaphragm EMG could be recorded on paper at a time. A Hans Rudolph heated pneumotachograph (model 3700) was attached to the endotracheal tube for measurement of both inspiratory and expiratory flow and tidal volume. The experimental preparation is shown in Figure 1.

The following variables were measured continuously throughout the experiment: airway pressure, intraabdominal pressure, tidal volume, flow, and the raw and averaged EMG signals of one hemidiaphragm. After a stabilization period of 30 min, the dog's airway was occluded by clamping the endotracheal tube (Figure 1) at end expiration. The occlusion was maintained for three consecutive inspiratory efforts (Figure 2). The occlusion maneuver was performed to assess the contribution of the ipsilateral hemidiaphragm to total inspiratory effort (see subsequent text). The clamp was then released. After the occlusion maneuvers, either 0.5% bupivacaine or normal saline solution in a volume of 0.3 mL/kg body wt was injected through an interpleural catheter. The ipsilateral EMG was recorded. Occlusion maneuvers of the airway were repeated every 5 min for 30 min. The contralateral EMG was then measured, and baseline measurements for that hemidiaphragm were made as described earlier. The corresponding interpleural catheter was injected with either bupivacaine or saline solution. Occlusion maneuvers of the airway were again repeated every 5 min for 30 min. Interpleural bupivacaine was injected on nine occasions and normal saline solution on four occasions in an attempt to obtain a 2:1 distribution of active treatment versus placebo. Two dogs received bupivacaine bilaterally.

At the end of the experiment, the dog was killed with an intravenous injection of KCl. Bilateral thoracotomies were done to assess the location of the interpleural catheter and to determine the presence of lung trauma that may have occurred during the insertion of the catheter. The results were classified into three categories:

1. Complete loss of nerve conduction. This was indicated by complete loss of phasic EMG activity in the ipsilateral diaphragm.
2. Partial loss of nerve conduction. The EMG of the ipsilateral diaphragm decreased (but was not abolished), with no corresponding decrease in occlusion pressure.
3. No effect. No change in EMG or occlusion pressure or corresponding changes in both variables.

Results

In total, interpleural bupivacaine was injected on nine occasions and normal saline solution on four occasions. In one dog, an adequate EMG signal could not be obtained from the left hemidiaphragm because of electrocardiographic interference. Thus, only one side was injected in this animal. In five of nine experiments in which bupivacaine was injected, there was complete loss of EMG activity on the side of the

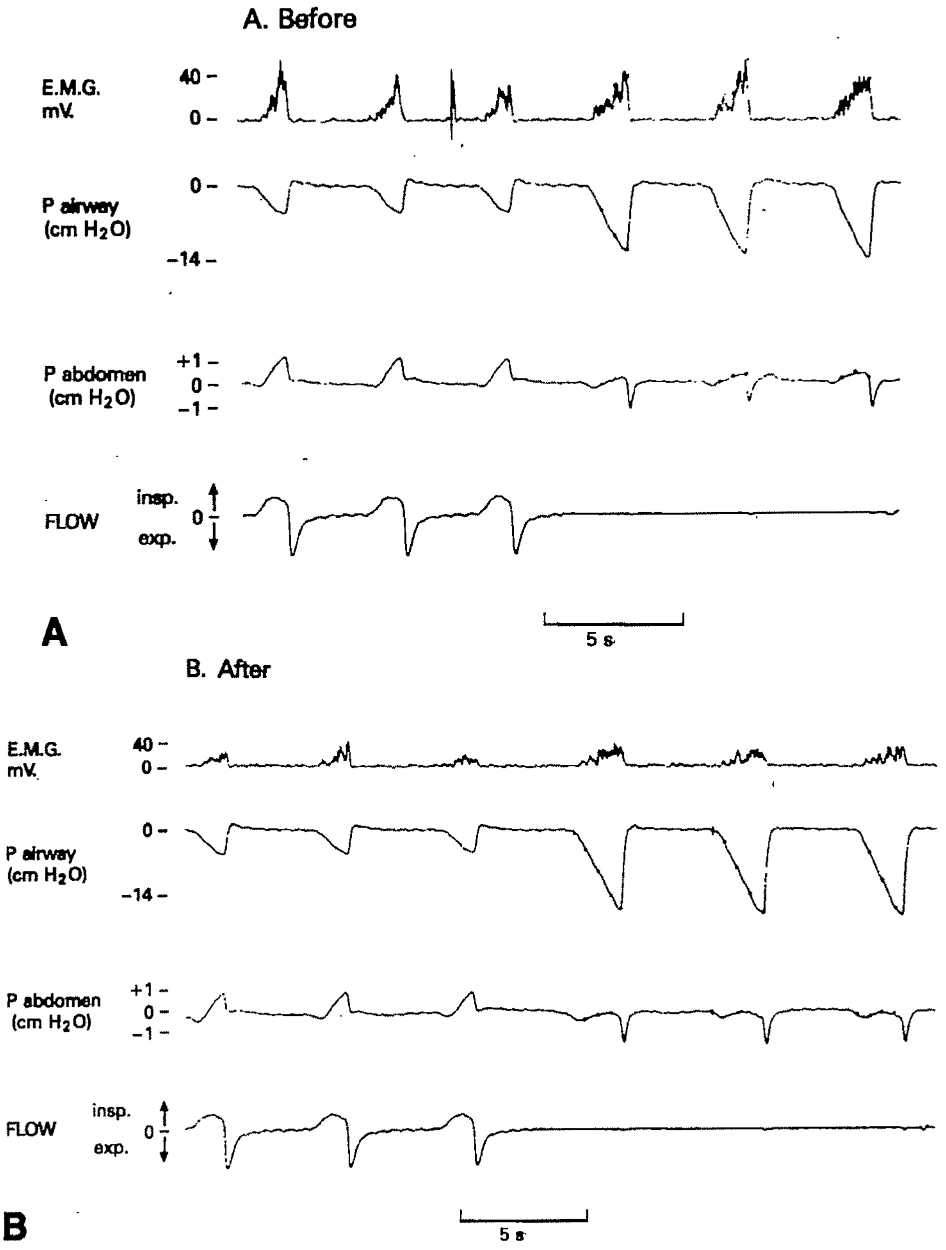

Figure 2. An example of a decrease in the amplitude of the diaphragmatic electromyographic (E.M.G.) signal: (**A**) before and (**B**) 30 min after injection of 0.5% bupivacaine. Note that the ipsilateral electromyographic signal is reduced despite a greater respiratory drive, as expressed by a more negative inspiratory pressure during occlusion. P airway, airway pressure; P abdomen, intraabdominal pressure.

injection. In two of the experiments with bupivacaine, there was no visible change in EMG, and the inspiratory intraabdominal pressures remained positive. In the remaining two experiments with bupivacaine, there was a decrease in the intensity of EMG signal with no corresponding decrease in occlusion pressure. An example is shown in Figure 2.

The most striking observation was made in the two dogs that received bilateral interpleural injections of bupivacaine. These dogs developed paradoxical respirations with negative inspiratory intraabdominal pressures, as shown in Figure 3. In one dog there was a complete loss of EMG activity bilaterally; in the other dog paradoxical respiration occurred with loss of EMG in one hemidiaphragm and a diminished, although still present, EMG in the other hemidiaphragm. In the normal saline solution group, there was no change in the EMG and no change in inspiratory intraabdominal pressure.

At the conclusion of all of the experiments, the interpleural catheters were all located in the pleural space. The position of the catheter tip was variable,

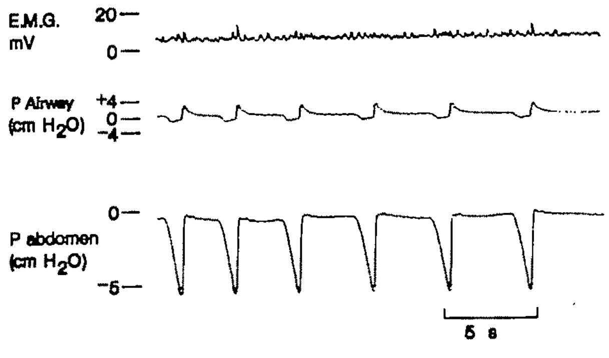

Figure 3. Spontaneous breathing in a dog that received 0.5% bupivacaine in both interpleural catheters. There is almost no electromyographic (E.M.G.) activity. The animal has highly negative intraabdominal pressures (P abdomen), even during spontaneous ventilation. P Airway, airway pressure.

with some located posteroapically and others more posterocaudally. There was no evidence of lung trauma in any dog.

Discussion

The pressure generated at the airway during occlusion at functional residual capacity is a reflection of the collective activity of all inspiratory muscles and is used as a measure of respiratory drive (12). The electrical activity recorded from the EMG wires is a reflection of activity in the sampled muscle. The latter may change, either because of local block of the motor fibers supplying that muscle (this is the response being sought) or because of global changes in respiratory drive responding to a change in level of anesthesia, temperature, etc. In the event that changes in measured EMG are related to changes in global drive, both EMG and occlusion pressure should change in the same direction and by roughly the same extent. Changes in EMG not matched by similar changes in occlusion pressure would indicate a selective action on the motor supply of the sampled muscle.

The results show that diaphragmatic dysfunction can result from interpleural injection of bupivacaine in the dog. The observation of paradoxical respirations with negative intraabdominal pressures provides unequivocal evidence of this. The negative intraabdominal pressure is produced by the continued inspiratory activity of the intercostals, resulting in a paradoxical upward, rather than the normal downward, displacement of the diaphragm. The volume of bupivacaine that was injected was small (0.3 mL/kg body wt) in an attempt to use the comparable volume used in humans (20 mL for a 70-kg subject). In addition, the dogs were kept supine during the experiment. No attempt was made to tip the animal one way or the other, to direct the local anesthetic toward the phrenic nerve.

The anesthetic used for the experiment may have affected the results obtained, in that halothane has negative inotropic properties on diaphragmatic muscle in both the dog and the rat (13,14). Halothane progressively decreases the transdiaphragmatic pressure generated by phrenic nerve stimulation in both animal models. This phenomenon appears to be caused by a negative inotropic action, as opposed to interference with neuromuscular transmission. Nevertheless, EMG activity is preserved, although diminished, at levels up to 2% inspired halothane concentration. Halothane may have decreased the baseline EMG measurements in the experiments, but the concentrations used (1% inspired) could not by themselves cause loss of EMG activity. Also, there was no evidence of diaphragmatic dysfunction during baseline measurements before injection of bupivacaine.

The EMG signal can be affected because of technical reasons, such as blood or fluid accumulation around the diaphragmatic wires. It was believed that this was unlikely to have caused the changes seen because of the lack of changes seen in the group that received interpleural normal saline solution and because the change in EMG activity was so closely related to the injection of bupivacaine.

Diaphragmatic dysfunction can be caused by laparotomy in both humans and dogs with noxious visceral stimulation (i.e., either by cholecystectomy or simply by applying traction to the gallbladder bed) (15,16). Care was taken during the surgical preparation to minimize any unnecessary visceral manipulation. At the end of surgical preparation, with the abdomen closed, all dogs were breathing in a normal manner, generating positive intraabdominal pressures during inspiration. Again, no animal had evidence of diaphragmatic dysfunction before interpleural injection.

Is the dog an appropriate model to use for this experiment? In both dogs and humans, the phrenic nerve follows a similar course through the thorax to the diaphragm. In both species, there is a layer of mediastinal pleura separating the phrenic nerve from the pleural space (17,18). In the dog, the phrenic nerve splits into three main branches (ventral, lateral, and dorsal) as it enters the diaphragm (17). The phrenic nerve in humans also splits into three branches: the anterior, anterolateral, and posterior branches. The posterior/dorsal branch supplies the crural portion of the diaphragm (18). The dog, like humans, has a connection between each phrenic nerve and the sympathetic nervous system at the celiac plexus. The periphery of the diaphragm receives sensory innervation from the last several intercostal nerves in both humans and dogs, but the phrenic nerve is the only motor nerve to the diaphragm. Although there are differences in the shape of the thoracic cavity between humans and dogs, phrenic nerve anatomy and diaphragmatic innervation are quite similar.

It is possible that if the phrenic nerve is blocked at the site where it divides into its three branches, one or two of its branches may be blocked, leaving the remaining branches intact. In this experiment, the diaphragmatic wires were placed only in the costal portion of the diaphragm. Thus, isolated paralysis of the crural portion may not have been detected. Theoretically, it is possible to block a portion of the diaphragm and obtain partial dysfunction of the diaphragm. It need not be an "all-or-none" phenomenon.

It is important to note that the diaphragm is not one muscle; rather, it consists of two distinct muscles; the costal and crural portions. Both have different motor innervation, fiber composition, and embryologic origins. The diaphragm has a complex mechanical arrangement, with the costal and crural portions of the diaphragm acting as if they were mechanically arranged, partly in parallel and partly in series at functional residual capacity and gradually moving into a purely mechanical series as lung volume increases (19). During quiet respiration, the crural portion shortens more than the costal and also shortens before the costal portion begins to contract.

De Troyer et al. (20) have demonstrated that under the proper circumstances, isolated contraction of the costal portion of the diaphragm without contraction of the crural portion may result in paradoxic respiration with negative intraabdominal pressures (20). This may have occurred in one of the dogs in which EMG activity was still present in one hemidiaphragm, but paradoxical respiration was observed.

Qualitative changes in the EMG were observed in two dogs. The significance of this observation is not known, but one might speculate that this is a manifestation of partial phrenic nerve blockade.

In conclusion, diaphragmatic dysfunction can occur in dogs after interpleural administration of 0.5% bupivacaine. The factors that predispose diaphragmatic dysfunction to occur in one animal as opposed to another are not known. The exact site of phrenic nerve blockade is also not known. One cannot directly extrapolate from this experiment to the use of interpleural analgesia in humans. However, it should be determined whether complication can occur in humans, and if so, what are its incidence and significance.

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A Trial of Desmopressin to Reduce Blood Loss in Patients Undergoing Spinal Fusion for Idiopathic Scoliosis

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Desmopressin (DDAVP) has been reported to reduce bleeding in patients undergoing spinal fusion. To evaluate its efficacy in normal patients, 30 healthy young patients (ASA physical status I or II) undergoing spinal fusion for idiopathic scoliosis were randomly allocated to receive either 100 mL of physiologic saline solution (placebo group) or DDAVP (10 $\mu g/m^2$ of body surface area) (DDAVP group) in a prospective, double-blind trial. Intraoperative blood loss was measured by weighing sponges and suction drainage and postoperative bleeding by wound drainage. The amount of blood loss expressed as a percent of the estimated blood volume was similar in both groups during the intraoperative period (67.0% ± 28.8% [mean ± SD] placebo group vs 57.4% ± 26.5% DDAVP group), the postoperative period up to 24 h (32.5% ± 6.4% placebo group vs 31.1% ± 10.6% DDAVP group), and both periods (94.3% ± 29.4% placebo group vs 88.2% ± 30.7% DDAVP group). With the dose used in our study, we conclude that DDAVP does not reduce surgical bleeding in patients undergoing spinal fusion for idiopathic scoliosis.

(Anesth Analg 1992;75:405–10)

Surgery for scoliosis is a procedure associated with large blood loss, during which patients may lose their total estimated blood volume or more (1,2). Factors influencing bleeding are the extent of dissection; number of fused vertebrae; length of surgery; surgical technique used, including type of instrumentation, site, and size of bone graft and phase of operation in which it is obtained; and mean arterial blood pressure and pressure in the inferior vena cava (3,4). In patients with idiopathic scoliosis, hemostatic abnormalities may in some cases increase the bleeding problem. Despite a bleeding time that is usually within the normal range, half of these patients have abnormal platelets with a depressed aggregation in response to epinephrine and adenosine diphosphate (5). Furthermore, the collagen from patients with idiopathic scoliosis aggregates platelets only one-fourth as efficiently as the collagen from normal patients (6).

Desmopressin (DDAVP) is an analogue of the natural hormone vasopressin with an antidiuretic/pressor ratio that is approximately 2000- to 3000-fold greater than that of vasopressin. Substitution of D-arginine for L-arginine in position 8 results in a markedly diminished pressor activity, or V_1 effect, whereas deamination of cystein in position 1 allows for an increase in the antidiuretic, or V_2, effect and increases the length of action, with a half-life of 2.5–4.4 h (7,8). Through its V_2 effects, desmopressin also causes endothelial cells to release von Willebrand factor, tissue-type plasminogen activator, and certain prostaglandins. An increase in the release of von Willebrand factor, particularly the higher molecular-weight multimers, accounts for the hemostatic activity of DDAVP in patients with uremia, chronic liver disease, and certain types of von Willebrand's disease by promoting platelet adhesiveness to the vascular endothelium (9–12). Desmopressin has also been reported to minimize intraoperative blood loss in patients undergoing cardiac surgery with extracorporeal circulation, although the results have been variable, with some authors finding a decrease in bleeding, whereas others have found no beneficial effects (13–16).

Kobrinsky et al. (17) reported that a single dose of 10 $\mu g/m^2$ of body surface area of DDAVP adminis-

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tered immediately after induction of anesthesia could reduce intraoperative bleeding by 30% in patients undergoing spinal fusion surgery with a normotensive anesthesia technique. However, firm conclusions with regard to patients with idiopathic scoliosis cannot be drawn from this study, because patients enrolled had either idiopathic scoliosis or scoliosis secondary to cerebral palsy or neuromuscular disorders. In spinal fusion surgery, the use of DDAVP can be hazardous because its V_2 effects may worsen the syndrome of inappropriate antidiuretic hormone secretion already present in that type of surgery (18–20). The aim of this study was to evaluate the efficacy of DDAVP in reducing blood loss in spinal fusion surgery for idiopathic scoliosis.

Methods

Thirty healthy (ASA physical status I or II) consecutive patients (28 female, 2 male) with idiopathic scoliosis scheduled for spinal fusion who met the inclusion criteria were randomly allocated (block randomization) to receive at the time of skin incision either 100 mL of physiologic saline solution (placebo group) or DDAVP (10 $\mu g/m^2$ body surface area) (maximal dose 20 μg) in the same amount of saline solution (DDAVP group) infused in 20 min. Blood volume was estimated at 60 mL/kg in the female subjects and at 65 mL/kg in the male subjects (21). If the patient was obese, body surface area and estimated blood volume were calculated by using the higher acceptable body weight for height (22). The design was double blind, and the surgeon, the anesthesiologist, and the investigator collecting the experimental data were all unaware of which solution was administered. Patients were not considered for inclusion in the study if a different surgical technique was used (i.e., the absence of wound drainage to allow postoperative bleeding measurement). Patients were also excluded if they had one of the following: history of a bleeding diathesis, ingestion of drugs known to interfere with hemostasis, abnormal bleeding time (>9 min), prolonged (>36 s) activated partial thromboplastin time, prolonged (>25 s) thrombin time, prolonged (>16 s) prothrombin time, or a low platelet count ($<150 \times 10^9$/L). This protocol was accepted by the ethics committee of our institution, and informed consent was obtained for each patient.

During surgery, patients were monitored with a cardioscope, a pulse oximeter, and an automated oscillometric blood pressure device. An arterial catheter was installed in the radial artery (20 gauge) and a central venous catheter introduced into the right internal jugular vein (16 gauge). Heart rate and blood pressure were recorded before the induction of anesthesia and every 5 min thereafter until the end of anesthesia. Central venous pressure, temperature, and urine output were recorded every hour during surgery. All patients were positioned on a Harrington frame. Anesthesia with normotension (65–85 mm Hg mean arterial pressure) was achieved with nitrous oxide, isoflurane, intravenous fentanyl (10–15 μg/kg), and pancuronium. Appropriate minute ventilation and fresh gas flows were calculated to maintain normocarbia with a coaxial circuit. Maintenance fluid requirements and third space losses were replaced with lactated Ringer's solution (6–10 $mL \cdot kg^{-1} \cdot h^{-1}$) to maintain the central venous pressure between 4 and 8 mm Hg. Surgical blood losses were compensated with lactated Ringer's solution up to 20%–30% of the estimated blood volume with a ratio of 3:1 and with packed red blood cells diluted in normal saline solution or banked autologous blood (eight patients in the placebo group and seven patients in the DDAVP group) for blood losses exceeding 20%–30% of the estimated blood volume. For patients with homologous blood transfusion, fresh-frozen plasma was administered after loss of 50%–100% of the estimated blood volume.

The skin was infiltrated with 20–250 mL of a solution of epinephrine 1:1,000,000, and all patients underwent a Cotrel-Dubousset technique executed by one of the two surgeons participating in the study. In brief, exposition of the bony elements was done from the upper vertebra to the lower vertebra chosen to be fused. After harvesting cortical and cancellous bone from the right iliac crest, hooks were inserted. Decortication of laminae, facet joints, and transverse processes was performed at every level, and rods were inserted with a derotation maneuver as indicated. A wake-up test was performed, and bone graft was packed at all levels to be fused. Wound drainage was inserted before closure.

Bleeding time was measured before surgery with a Simplate (Organon Teknika, Durham, N.C.). Blood samples were obtained for the measurement of hemostatic values before and 20 min after DDAVP administration by venipuncture (21-gauge needle) or from the central venous catheter (first 10 mL discarded) and sent to the laboratory in silicone-coated vacutainer tubes (Becton Dickinson, Rutherford, N.J.) containing 105 mM buffered citrate, for a final ratio of one part anticoagulant to nine parts of blood. After two consecutive centrifugations at 12,000*g* for 10 and 20 min, respectively (4°C), platelet-poor plasma was fast-frozen and kept at −70°C until used. Coagulation tests were done with a Fibrintimer 10 (Behring Diagnostics, Montreal, Canada). Prothrombin time, partial thromboplastin time, and thrombin time (Organon Teknika) were performed as recommended by the manufacturer. Factors V and VIII were measured in a one-stage assay. Von Willebrand factor was measured by quantitative immunoelectrophoresis (23). Euglobulin lysis time and fibrin plate lysis were measured as described previously (24,25). Hemostasis tests were considered abnormal if their results exceeded the mean plus two standard deviations of results obtained from 20 regular normal volunteer donors. Samples for the measurement of hemoglobin, hematocrit, and blood and urinary sodium and osmolality were taken before DDAVP administration and at 1, 8, 14, and 24 h after skin incision. Hemoglobin, hematocrit, and platelet counts were determined with Technicon H-1 (Tarrytown, N.Y.). Blood and urinary osmolality were determined by the freezing-point depression (Microosmometer, Advanced Instruments Inc., 3MO) and sodium levels in blood and urine were measured with an ion-specific electrode (ISE, Parallel American Monitor). Intraoperative blood loss was measured by weighing sponges and suction drainage, and postoperative bleeding by wound drainage (Snyder, Hemovac) during the next 24 h.

Data were analyzed for statistical significance with analysis of variance for repeated measures, followed by the Scheffé multiple-comparisons test, variance-covariance analysis, unpaired *t*-test, and χ^2 test with Yates' correction when appropriate. Statistical significance was determined at $P < 0.05$, and the number of patients was determined to detect a difference in blood loss of 30% with a β error of 0.2. Data are presented as mean ± SD.

Table 1. Clinical Characteristics of 30 Patients Undergoing Spinal Fusion for Idiopathic Scoliosis

	Placebo group (n = 15)	DDAVP group (n = 15)
Gender (F/M)	14/1	14/1
Age (yr)	15.1 ± 1.9	13.5 ± 1.9
Body surface area (m^2)	1.4 ± 0.1	1.5 ± 0.1
No. of obese pts	0	6[a]
Bleeding time (before surgery) (min)	5.1 ± 1.6	5.3 ± 2.0
Epinephrine used (mL of 1:1,000,000)	150 ± 45	130 ± 65
Minimal core temp (°C)	34.7 ± 0.7	34.9 ± 0.7
Curve angle (degree)	56.1 ± 13.8	54.3 ± 13.3
No. of fused vertebras	9.0 ± 1.6	9.7 ± 1.3
Length of surgery (h)	3.7 ± 0.7	4.1 ± 1.2
Crystalloids administered during surgery (L)	4949 ± 1196	5648 ± 1919
Diuresis ($mL \cdot kg^{-1} \cdot h^{-1}$)		
1st h of surgery	5.1 ± 1.2	1.2 ± 1.2[a]
2nd h of surgery	1.6 ± 2.5	0.4 ± 0.3[a]
3rd h of surgery	1.0 ± 1.0	0.6 ± 0.5[a]
4th h of surgery	0.7 ± 0.7	0.7 ± 0.5
During 24 h (mL/kg)	30.9 ± 11.9	22.9 ± 8.1[a]

DDAVP, desmopressin; F, female; M, male; pts, patients.
Mean ± SD.
[a] Placebo group different from DDAVP group, $P < 0.05$.

Results

Only one patient could not participate in the study because of a prolonged bleeding time. The two groups were comparable for gender distribution, age, body surface area, minimal temperature, number of fused vertebrae, curve angle, length of surgery, preoperative bleeding time, and quantity of epinephrine used (Table 1). There were no obese patients in the placebo group compared with six in the DDAVP group. Heart rate and central venous pressure were not different between the two groups. The mean arterial pressure was lower in the DDAVP group than in the placebo group for up to 45 min, with the largest difference at 30 min (67.6 ± 9.3 vs 79.3 ± 7.4 mm Hg, respectively) and was comparable in both groups thereafter. All hematologic variables were in the normal ranges and similar in both groups before the intervention.

Desmopressin induced a significant increase in Factor VIII coagulant (+61.2% ± 68%; $P < 0.001$) and in von Willebrand factor (+44.4% ± 64.2%; $P < 0.005$). Both groups had a comparable decrease in their platelet count during surgery (Table 2). The increase in Factor VIII coagulant and in von Willebrand factor for the obese patients in the DDAVP group (+69.7% ± 64.2% and +46.3% ± 57.1%, respectively) was comparable to that observed for the nonobese patients in the same group (+55.0% ± 74.4% and +42.9% ± 73%, respectively).

The amount of blood loss as a percent of the estimated blood volume was similar in both groups for the intraoperative period (i.e., 67.0% ± 28.8% [placebo group] vs 57.4% ± 26.5% [DDAVP group]), the postoperative period up to 24 h (32.5% ± 6.4% [placebo group] vs 31.1% ± 10.6% [DDAVP group]), and both periods (94.3% ± 29.4% [placebo group] vs 88.2% ± 30.7% [DDAVP group]) (Table 3). The power of the study to detect a difference of 30% in blood losses between the two groups was close to 1 for each of these three values. The total amount of blood loss for the obese patients in the DDAVP group was similar to that of the nonobese patients in the same group (i.e., 97.7% ± 34.4% of estimated blood volume, or 3128 ± 1125 mL, for normal patients, compared with 75% ± 19% of estimated blood volume, or 2887 ± 791 mL, for the obese patients). The total amount of blood loss for patients operated on by one of the two surgeons was 93.6% ± 30.2% of estimated blood volume, or 3161 ± 1142 mL (10 patients in the DDAVP group and 13 in the placebo group), and 95.2% ± 36.0% of estimated blood volume, or 3056 ± 926 mL, for the other surgeon (five patients in the

Table 2. Hemostatic Variables in 30 Patients

	Before surgery		After treatment		% Change	
	Placebo group	DDAVP group	Placebo group	DDAVP group	Placebo group	DDAVP group
Platelets (×10^9/L)	295 ± 60	288 ± 59	234 ± 47[a]	252 ± 50	−21.3 ± 13.6	−19.1 ± 13.4
Prothrombin time (s)	12.8 ± 1.4	12.5 ± 0.8	13.6 ± 1.3	13.7 ± 1.3	6.8 ± 6.8	8.2 ± 7.1
Partial thromboplastin time (s)	31.8 ± 3.3	31.7 ± 3.5	33.4 ± 3.5	32.9 ± 3.8	6.0 ± 11.0	4.1 ± 6.9
Thrombin time (s)	20.3 ± 1.3	20.4 ± 1.5	22.1 ± 1.5	21.7 ± 2.3	6.9 ± 9.1	6.9 ± 9.0
Factor V (U/mL)	0.75 ± 0.48	0.65 ± 0.14	0.47 ± 0.14	0.65 ± 0.29[b]	−26.3 ± 26.0	7.0 ± 54.6
Factor VIII coagulant activity (U/mL)	0.81 ± 0.27	0.80 ± 0.34	0.66 ± 0.22	1.22 ± 0.58[b]	−17.2 ± 18.9	61.2 ± 68.0[c]
von Willebrand factor antigen (U/mL)	0.91 ± 0.32	0.85 ± 0.40	0.72 ± 0.43	1.07 ± 0.51	−19.2 ± 41.6	44.4 ± 64.2[c]
Euglobulin lysis time (min)	286.0 ± 240.7	308.4 ± 242.4	317.1 ± 250.2	201.5 ± 52.5	34.2 ± 93.4	−19.7 ± 35.9
Fibrin plate lysis (mm^2)	62.2 ± 9.6	61.4 ± 13.6	55.9 ± 17.6	52.4 ± 16.9	−11.1 ± 27.0	−13.6 ± 19.9

DDAVP, desmopressin.
Mean ± SD.
[a] Significantly lower than the preoperative value, $P < 0.05$.
[b] Value in DDAVP group is significantly greater than in placebo group, $P < 0.05$.
[c] The increase is significantly greater in DDAVP group than in placebo group, $P < 0.005$.

Table 3. Bleeding and Transfusions in 30 Patients

	Placebo group	DDAVP group
Intraoperative blood losses and transfusions		
Total (mL)	2101 ± 884	1975 ± 905
Estimated blood volume (%)	67.0 ± 28.8	57.4 ± 26.5
Estimated blood volume per fused vertebra (%)	7.1 ± 2.9	6.0 ± 2.0
Packed red blood cells or autologous blood (U)	3.7 ± 2.1	3.5 ± 2.2
Plasma (U)	0.3 ± 0.5	0.4 ± 0.5
Postoperative blood losses and transfusions at 24 h		
Total	1029 ± 230	1056 ± 293
Estimated blood volume (%)	32.5 ± 6.4	31.1 ± 10.6
Estimated blood volume per fused vertebra (%)	3.4 ± 1.2	3.6 ± 1.1
Packed red blood cells or autologous blood (U)	1.0 ± 0.7	0.9 ± 0.9
Intraoperative and postoperative blood losses at 24 h		
Total	3130 ± 969	3031 ± 981
Estimated blood volume (%)	94.3 ± 29.4	88.2 ± 30.7
Estimated blood volume per fused vertebra (%)	10.6 ± 3.7	9.8 ± 2.2
Hemoglobin (g/L)		
Preoperative	122.2 ± 17.5	125.9 ± 14.1
Recovery room	101.3 ± 15.3	105.5 ± 11.8
24 h postoperative	94.6 ± 12.9	94.9 ± 16.1

DDAVP, desmopressin.
Mean ± SD; the two groups were comparable for all values.

DDAVP group and two in the placebo group). No patient in either group needed a second surgical procedure to control postoperative bleeding.

There was a significant difference in diuresis during the first 3 h of surgery ($P < 0.05$) and during the entire 24 h (30.9 ± 11.9 [placebo group] vs 22.9 ± 8.1 [DDAVP group]; $P < 0.05$) (Table 1). Variations of blood and urinary sodium and osmolality were similar in both groups. One patient in the DDAVP group had sodium <130 mEq/L 8 h after DDAVP, and 46% of all patients had serum osmolality <275 mOsm/kg H_2O at 24 h after skin incision (i.e., eight patients in the placebo group and six in the DDAVP group).

Discussion

In this study, we administered a single dose of DDAVP to patients with idiopathic scoliosis who had no known disorder of hemostasis and with normal preoperative coagulation tests. After DDAVP, both Factor VIII and von Willebrand factor increased significantly by 61.2% and 44.4%, respectively. However, the administration of DDAVP provided no real benefit, because it did not significantly reduce the total blood losses during the entire 24-h period; neither did DDAVP diminish intraoperative or postoperative blood transfusion requirements (Table 3).

It is surprising at first glance that bleeding was not decreased, considering the abnormalities of hemostasis often seen in patients with idiopathic scoliosis (5,6). An increase in von Willebrand factor by DDAVP should have improved hemostasis in these patients, because this factor mediates the adhesion of platelets to damaged endothelium (8). The absence of blood loss reduction by DDAVP may be explained by the fact that only patients without significant clinical bleeding disorders and with normal preoperative coagulation tests were enrolled in our study, thus possibly excluding patients who could have benefited most from a substance-enhancing hemostasis. However our patients represent the usual population undergoing surgery for idiopathic scoliosis, because the hemostatic abnormalities found in patients with idiopathic scoliosis seldom lead to a prolonged bleeding time or to clinical bleeding problems (6). This was well demonstrated during the course of our study when only one patient could not be enrolled because of abnormal preoperative coagulation tests. To date, most authors who administered DDAVP to reduce blood loss in patients without significant clinical bleeding disorders for uncomplicated surgery failed to demonstrate any beneficial effect (14–16). Our results differ from those of Kobrinsky et al. (17) who reported that DDAVP reduced the amount of intraoperative blood loss by 30% during scoliosis surgery; however, they studied a group of patients who had scoliosis of varying etiologies and found that DDAVP seemed more useful in patients with scoliosis secondary to neuromuscular disorders. There seems to be a difference in the reduction of blood loss by DDAVP between patients with idiopathic scoliosis and patients who have developed scoliosis because of an underlying neuromuscular pathology (17). Certain platelet anomalies have been reported in patients with Duchenne type muscular dystrophy, particularly a marked increase in the calcium and phosphorus content of platelets (26). It is possible that there is an abnormal bleeding process in the muscle tissue of these patients and that this particular type of bleeding may be helped by the use of DDAVP.

The following factors may account for the fact that DDAVP did not reduce bleeding in normal patients undergoing spinal fusion for idiopathic scoliosis. The epinephrine liberated during the surgical stress and administered subcutaneously before surgical incision might have caused an increase in von Willebrand factor in both groups, considerably reducing the beneficial effect of DDAVP (27). It is also possible that under general anesthesia or during surgery, or both, the release of Factor VIII and von Willebrand factor usually seen after the administration of DDAVP is incomplete or that there is an increased consumption of these factors during the surgical period. In this study, the increase in Factor VIII and von Willebrand factor (61% and 44%, respectively) after DDAVP was comparable to results described in patients who received a dose of 0.3 μg/kg of DDAVP during surgery under general anesthesia (50% and 35%, respectively) (28). However this increase is relatively modest compared with that usually observed either in normal patients or in patients with von Willebrand's disease who received the same dose of DDAVP (0.3 μg/kg) outside the surgical period, which is then 400% and 300% for Factor VIII and von Willebrand factor, respectively (12). Our DDAVP group included six obese patients versus none in the placebo group, and DDAVP dosage was established by using the body surface area determined with the higher acceptable weight for height and up to a maximal dose of 20 μg. It is possible that with this method, the dose of DDAVP administered in the obese patients was inferior to the optimal dose. However we do not think that this is the case for the following reasons: the increase in Factor VIII and von Willebrand factor for the obese patients in the DDAVP group was similar to that for the nonobese patients in the same group (i.e., 69.7% ± 64.2% and 46.3% ± 57.1%, respectively, for the obese patients compared with 55.0% ± 74.4% and 42.9% ± 73%, respectively, for the nonobese patients). Furthermore, the bleeding in the obese patients in the DDAVP group was not increased compared with that of the nonobese patients in the same group (i.e., 75% ± 19% of estimated blood volume, or 2887 ± 791 mL, in the obese patients compared with 97% ± 34% of estimated blood volume, or 3128 ± 1125 mL, in the nonobese patients). Certain side effects of DDAVP may have counterbalanced the otherwise beneficial rise in the release of von Willebrand factor. The vasodilating properties of DDAVP could have possibly increased the bleeding process, at least during the first hour after its administration (29,30). Also, the release of tissue-type plasminogen activator may have produced a fibrinolysis that we were unable to detect (8). Finally, the blood vessels in bone are noncollapsible structures that are supported by the bone lamellae and consequently will remain open when the bone is cut. This type of bleeding is particularly difficult to control and may not be readily influenced by substances that modify hemostasis.

The inability to reduce bleeding during the postoperative period could be due to the administration of a single dose of DDAVP, because in a normal individual the half-life of Factor VIII and von Willebrand factor after injection of DDAVP is 266 and 563 min, respectively (12). There is no evidence, however, that multiple doses would have helped to lower blood loss during the postoperative period, given the lack of response in the intraoperative period and the usual reduction in efficiency of DDAVP with increasing number of doses administered. Indeed, DDAVP does not produce an increase in synthesis of Factor VIII and von Willebrand factor but only releases existing stocks of these factors, which explains the rapid occurrence of tachyphylaxis (12).

Desmopressin is a potent vasodilator with a direct muscular effect that is partially modulated by constricting and dilating prostaglandins (29,30). In this study, the observed decrease in blood pressure was without consequence, because the maximal difference in mean blood pressure between the two groups was only 12 mm Hg. A decrease in diuresis due to DDAVP was evident for only a short period after its administration, because patients in the placebo group had a progressive reduction in diuresis, with mean values of <1 mL·kg^{-1}·h^{-1} after the third hour of surgery. There was no increase in the incidence of hypoosmolality caused by DDAVP, because the number of patients with a serum osmolality of <275 mOsm/kg H_2O at 24 h was comparable in both groups.

In conclusion, with the dose used in our study, DDAVP does not reduce surgical bleeding in patients without a known bleeding diathesis undergoing spinal fusion for idiopathic scoliosis.

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Effect of Desmopressin Acetate on Hindlimb Perfusion Pressure in Rats: What Is the Mechanism?

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Desmopressin acetate (DDAVP) is a synthetic analogue of vasopressin used to promote hemostasis and reduce postoperative blood loss. Desmopressin acetate can cause hypotension in humans. Our study evaluated the hemodynamics of rapid administration of DDAVP into the isolated hindlimb in live rats and assessed this response after pretreatment with various antagonists. Thirty male Sprague-Dawley rats (350–450 g) were given intraperitoneal pentobarbital anesthesia (50 mg/kg). Perfusion was set at a rate that gave a control mean hindlimb perfusion pressure (HPP) of 100–120 mm Hg. Rats were assigned to five groups ($n = 5$, each group), with each rat serving as its own control. As a control, saline solution (in volumes equivalent to those used for the antagonists) was injected into the hindlimb preparation before the agonist injections. Each group received both the clinical preparation of DDAVP (i.e., with preservative) and a laboratory preparation of DDAVP in doses of 0.3–3 ng. Group 1 was tested before and after injection of saline solution control; group 2, before and after propranolol (0.5 mg/kg); group 3, before and after meclofenamate (1.5 mg/kg), a cyclooxygenase inhibitor; group 4, before and after nitroarginine (5 mg/kg), an inhibitor of nitric oxide synthesis; and group 5, before and after atropine sulfate (1 mg/kg). Chlorobutanol (25–75 μg), the preservative in the clinical preparation of DDAVP, was tested for changes in HPP in five rats similarly prepared. Systemic mean arterial pressure remained constant during the study. The HPP decreased with increasing doses of the clinical preparation of DDAVP, compared with saline solution controls, whereas no change occurred with the laboratory preparation of DDAVP. There were no changes after meclofenamate, chlorobutanol, or propranolol with either clinical or laboratory DDAVP; however, an additional significant decrease in HPP occurred with both atropine and nitroarginine ($P < 0.001$) for only the clinical preparation of DDAVP. We conclude that the clinical preparation of DDAVP, but not the laboratory preparation of DDAVP, causes significant dose-dependent vasodilation of the hindlimb vascular bed in the live male rat. The mechanism of this vasodilation is a direct action on vascular smooth muscle (nitric oxide studies) or receptor activity (atropine studies) or V_2-receptor agonism.

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Desmopressin acetate (1-desamino-8-D-arginine vasopressin) (DDAVP) is a synthetic analogue of vasopressin. It is used clinically in the treatment of diabetes insipidus (1), hemostasis and postoperative bleeding in patients with platelet dysfunction (2,3), and platelet dysfunction associated with cardiopulmonary bypass (4).

Desmopressin acetate also produces hypotension (5–8). We recently described 16 patients undergoing cardiac surgical procedures who were prospectively randomized into two groups to study the hemodynamic and possible histamine-releasing effects of DDAVP administration after cardiopulmonary bypass. We concluded that DDAVP at 0.3 μg/kg is a potent vasodilator when administered intravenously and that histamine is not involved (8).

Previous work examined possible roles of mediators or receptors that may be involved in DDAVP-induced vasodilation. Bichet et al. (5) hypothesized that stimulation of extrarenal V_2-like receptors by DDAVP results in hypotension. The clinical preparation of DDAVP decreases arterial blood pressure in the anesthetized rat (Jahr J, Kuchta K, Texidor M, Stevens K; personal communication) and relaxes isolated segments of aorta and pulmonary artery (9). Johns (9) has shown, using both in vitro rabbit and rat aortic root strips, that neither V_1- or V_2-antagonists nor H_1- or H_2-blockers have any mediating effects on DDAVP-induced vasodilation, although cyclooxygenase inhibitors such as indomethacin may potentiate this vasodilation. No in vivo studies exist that

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confirm mediator involvement in the vasodilation or hypotensive actions of DDAVP.

In the present study, responses to the laboratory and clinical preparations of DDAVP were investigated in the hindlimb vascular bed of the anesthetized rat under constant flow conditions so that changes in hindlimb perfusion pressure directly reflected changes in vascular resistance, testing a variety of antagonists and a nitric oxide inhibitor, as well as the preservative in the clinical preparation of DDAVP.

Methods

After Animal Care Committee approval, 30 male Sprague-Dawley rats (350–450 g) were given intraperitoneal pentobarbital anesthesia (50 mg/kg). Supplemental doses of anesthetic were given as needed to maintain a uniform level of anesthesia. The animals were mechanically ventilated with room air enriched with oxygen delivered by a cannula into the trachea. Arterial blood gas samples were obtained periodically; ventilation and oxygenation were maintained at normal values. Polyethylene tubing for venous access was placed by cutdown into the jugular vein to allow administration of the volume required to maintain homeostasis. One of the axillary arteries was dissected and cannulated to monitor systemic mean arterial pressure. A cutdown and cannulation of the right carotid artery provided the source of arterial blood, which was fed to a Harvard peristaltic pump for perfusing blood to the hindlimb vascular bed. The inferior abdominal aorta was cannulated immediately above the bifurcation with polyethylene tubing through which the output of the Harvard pump was infused. Heparin (1000 U/kg) was administered intravenously before perfusion. The hindlimb perfusion pressure and systemic mean arterial pressure were constantly monitored and recorded on a Grass model 7 polygraph. Perfusion was set at a rate that gave a control mean hindlimb perfusion pressure of 100–120 mm Hg. The animal's temperature was maintained at 37°C with a heating pad and monitored by rectal thermometer.

The clinical preparation of DDAVP (Rorer Pharmaceuticals, Fort Washington, Pa.) was supplied as a 4-μg/mL solution in 0.9% saline solution (pH adjusted to 4.0), containing chlorobutanol (1,1,1-trichloro-2-methyl-2-propanol) as preservative. The laboratory preparation of DDAVP (Peninsula Laboratories, Belmont, Calif.) was dissolved similarly in 0.9% saline solution, with the pH adjusted to 4.0 with HCl. Atropine sulfate, propranolol, and meclofenamate (Sigma Chemical Co., St. Louis, Mo.) were dissolved in 0.9% saline solution; these solutions were stored at −20°C and used within 2 wk.

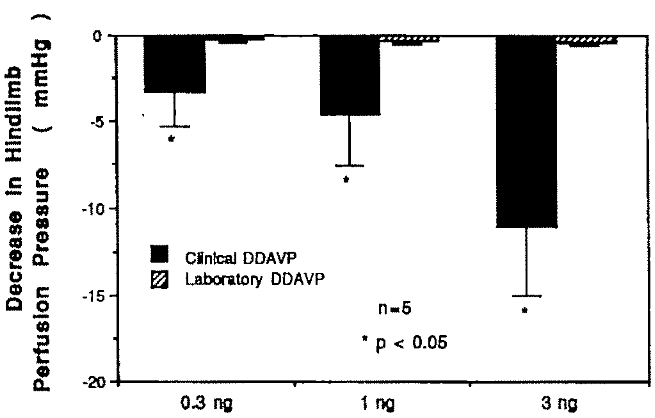

Figure 1. Comparison of laboratory and clinical preparations of DDAVP in the hindlimb vascular bed of the male rat.

N^{ω}-nitro-L-arginine (Aldrich, Milwaukee, Wis.) was dissolved at 10 mg/mL in 0.05 N HCl in 0.9% saline solution with sonication immediately before use. As a control, saline solution (in volumes equivalent to those used for the agonists) was injected into the hindlimb preparation before the agonist injections. The experiment with the antagonist was not performed until the hindlimb preparation was stable throughout the experiment. Responses to the laboratory preparation of DDAVP (0.3–3 ng) and the clinical preparation of DDAVP (0.3–3 ng) were first obtained in each rat. Then, 10 min after return to baseline, rapid administration into the perfusion circuit was performed in four different groups, respectively: meclofenamate (1.5 mg/kg IV), propranolol (0.5 mg/kg IV), atropine (1 mg/kg IV), or N^{ω}-nitro-L-arginine (nitroarginine) (5 mg/kg IV). Systemic mean arterial pressure was monitored for stability, and hindlimb perfusion pressure was recorded. As the hindlimb perfusion pressure is isolated, the systemic mean arterial pressure should remain constant in a normal, healthy laboratory rat preparation. If a rat did not maintain this hemodynamic stability, it was removed from the study. Statistical comparisons were made by using the *t*-test, with a P value ≤0.05 considered significant.

Results

All rat preparations remained stable, with no changes in systemic mean arterial pressure. Rapid administration of the clinical preparation of DDAVP into the perfusion circuit elicited dose-dependent decreases in hindlimb perfusion pressure, compared with saline solution controls ($P < 0.05$) (Figure 1). Decreases in hindlimb perfusion pressure ranged from 3 to 11 mm Hg; however, administration of the laboratory preparation of DDAVP did not cause a significant

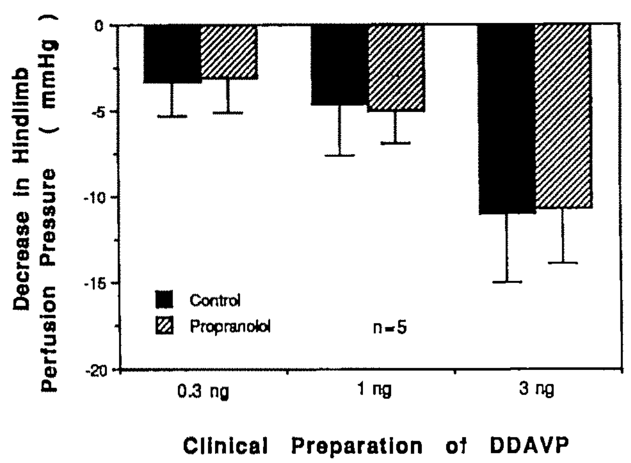

Figure 2. Effect of propranolol on the clinical preparation of DDAVP in the hindlimb vascular bed of the male rat.

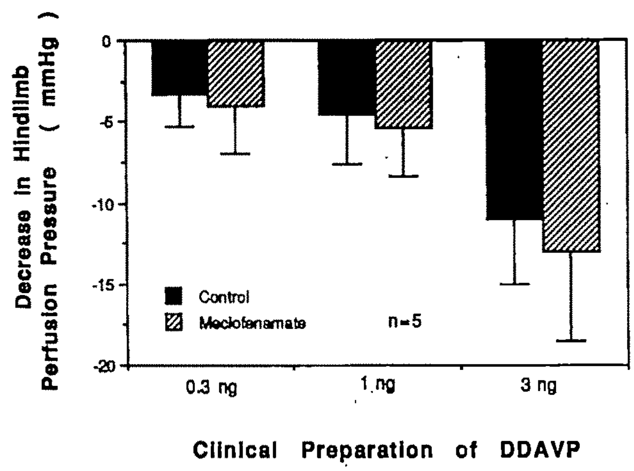

Figure 3. Effect of meclofenamate on the clinical preparation of DDAVP in the hindlimb vascular bed of the male rat.

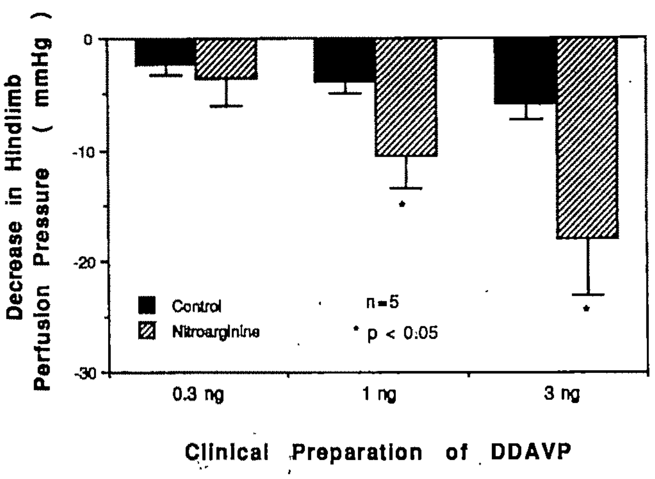

Figure 4. Effect of nitroarginine on the clinical preparation of DDAVP in the hindlimb vascular bed of the male rat.

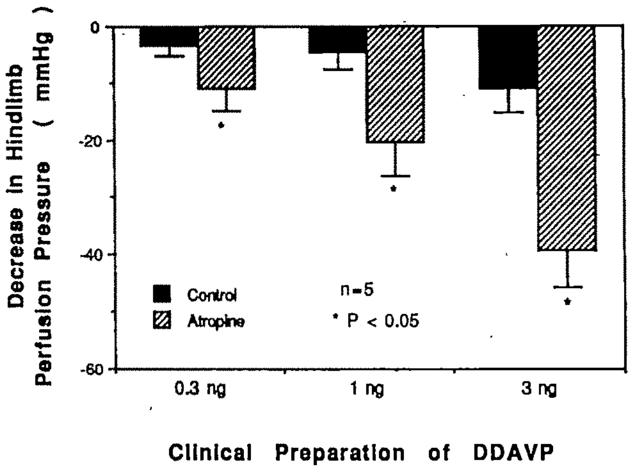

Figure 5. Effect of atropine on the clinical preparation of DDAVP in the hindlimb vascular bed of the male rat.

decrease in hindlimb perfusion pressure (Figure 1). The responses to both the laboratory preparation and the clinical preparation of DDAVP were not modified by propranolol (Figure 2), or meclofenamate (Figure 3); however, an additional significant decrease in hindlimb perfusion pressure with both atropine and nitroarginine was noted ($P < 0.001$) for the clinical preparation of DDAVP only (Figures 4 and 5). Chlorobutanol caused no change in hindlimb perfusion pressure.

Discussion

Salzman et al. (4) reported that patients undergoing various open-heart procedures had reduced perioperative blood loss when DDAVP was administered prophylactically. Desmopressin acetate is now used in some patients undergoing cardiopulmonary bypass, because this tends to degranulate platelets and to decrease their function (10).

Desmopressin acetate has few adverse effects (5). Most frequently noted is mild skin vasodilation, observed as facial flushing (6). This may be due to systemic release of prostacyclin (6). Desmopressin acetate is also known to produce hypotension (5–8). In our clinical study, rapid intravenous infusion of DDAVP after adult cardiopulmonary bypass revealed that DDAVP is a potent vasodilator and can cause significant hypotension (7). Further, in our clinical study, 16 patients undergoing cardiac surgical procedures were prospectively randomized into two groups to study the hemodynamic and histamine-releasing effects of DDAVP administration after cardiopulmonary bypass. We concluded that DDAVP at 0.3 μg/kg is a potent vasodilator when administered intravenously and that histamine is not involved (8).

Other mediators or receptors that may be involved in the DDAVP-induced vasodilation have been examined. Bichet et al. (5) reported no alteration in arterial blood pressure in patients with congenital diabetes insipidus who are congenitally devoid of V_1- and V_2-receptors. In contrast, in patients with central nephrogenic diabetes insipidus with intact V_1- and V_2-receptors, DDAVP administration lowered arterial blood pressure. Bichet et al. (5) hypothesized that stimulation of extrarenal V_2-like receptors by DDAVP results in hypotension. Recent studies have shown that DDAVP decreases arterial blood pressure in the anesthetized rat (Jahr J, Kuchta K, Texidor M, Stevens K; personal communication) and relaxes isolated segments of the aorta and pulmonary artery (9). Johns (9) has shown, using both in vitro rabbit and rat aortic root strips, that neither V_1- or V_2-antagonists nor H_1- or H_2-blockers have any modulating effects on DDAVP-induced vasodilation with either endothelium-intact or denuded vessels. The relaxation was partially dependent on intact endothelium and was potentiated by indomethacin, an inhibitor of cyclooxygenase (9). Chlorobutanol had no vasoactive effects (9). Unfortunately, Johns' (9) in vitro model represents capacitance and not resistance vessels, which may not be an appropriate model for testing vasodilation. No in vivo studies exist that confirm mediator involvement in DDAVP vasodilation.

The prophylactic or therapeutic administration of DDAVP in complicated cardiac surgery has been demonstrated to decrease blood loss perioperatively (4). However, DDAVP is not effective in decreasing blood loss in pediatric or adult patients undergoing uncomplicated cardiac surgery (10,11). Increased risk of early graft closure in patients undergoing coronary artery bypass grafting after DDAVP administration has also been reported (12), although no complications of this type were reported by Hackmann et al. (13). Current debate exists, therefore, over both the safety and efficacy of DDAVP in decreasing blood loss after cardiac surgery (14,15). If DDAVP is used, caution should be exercised after DDAVP administration owing to its potent vasodilator properties (8).

These results demonstrate that the clinical preparation of DDAVP has vasodilator activity in the hindlimb vascular bed of the rat and that responses to this preparation are not dependent on activation of β-adrenergic receptors or release of vasodilator prostaglandins. The experiments with nitroarginine, an inhibitor of nitric oxide synthesis from L-arginine, and atropine suggest that our DDAVP-induced vasodilator responses were dependent in part on the release of nitric oxide or a related nitroso compound derived from L-arginine or muscarinic receptor blockade, or both. The clinical preparation of DDAVP contains chlorobutanol as preservative, but the latter did not have vasoactivity. The two preparations were similar in terms of vehicle (0.9% saline solution), concentration, and pH.

Our results conflict with those of Johns (9), who found DDAVP-induced relaxation to be partially dependent on cyclooxygenase inhibitors. Johns did not assess muscarinic blockers or nitroarginine. We found no effect from meclofenamate. The difference may be in the experimental preparations, in vitro compared with in vivo, and the fact that the aortic strips that Johns investigated were not resistance vessels. Pulmonary vessels, although they are resistance vessels, often have differing drug response effects from systemic vessels. Only the clinical preparation of DDAVP, not the chlorobutanol nor the laboratory preparation of DDAVP, caused vasodilation. The additional vasodilation effects of atropine and nitroarginine suggest both a muscarinic receptor effect (vasoconstriction) and a direct vascular smooth muscle mechanism. A recent editorial review confirms the vasodilatory effects of nitroarginine, a nitric oxide congener: there is speculation that nitroarginine may even be an endothelium-derived relaxing factor (16). Another possibility for the vasodilation is direct V_2-receptor stimulation by the clinical preparation of DDAVP; however, we did not assess this. It is puzzling that the clinical preparation of DDAVP caused vasodilation when both the laboratory preparation and the chlorobutanol did not. Perhaps this difference may be explained by the concentrated DDAVP preparation or by impurities; however, from these data, one should not dismiss the results of the clinical preparation.

We conclude that the clinical preparation of DDAVP causes significant dose-dependent vasodilation of the hindlimb vascular bed of the live male rat, whereas the laboratory preparation of DDAVP does not. The vasodilatory mechanism is not β_2-adrenergic receptor agonism or blockade of the arachidonic acid cascade. Atropine and nitroarginine may augment the vasodilation, suggesting direct action on vascular smooth muscle, muscarinic receptor activity, or possibly, V_2-receptor agonism. The preservative of the clinical preparation of DDAVP, chlorobutanol, appears to have no vasodilatory effect. Therefore, the differences encountered may be a result of the DDAVP concentrate.

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Effects of Atipamezole, an α_2-Adrenoceptor Antagonist, on the Anesthesia Induced by Barbiturates and Medetomidine

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We studied the effects of atipamezole, an α_2-adrenoceptor antagonist, on hypnosis induced by medetomidine, an α_2-adrenoceptor agonist (1 mg/kg IP), and pentobarbital (40 mg/kg IP) by testing the righting reflex in the rat. The duration of antinociception was assessed with repeated pinch tests. Medetomidine-induced hypnosis and antinociception were inhibited by atipamezole at doses >0.1 mg/kg. Atipamezole restored the righting reflex at a dose ratio that was 1:10 or more to that of medetomidine used to induce hypnosis. Subcutaneous atipamezole (1.5 mg/kg) increased the duration of hypnosis induced by pentobarbital (40 mg/kg) and pentobarbital + medetomidine (0.3 mg/kg). Hypnosis induced by methohexital (60 mg/kg IP) was also prolonged by atipamezole. The capacity of atipamezole to reverse the effects of medetomidine is also reduced in the presence of barbiturates. Thus, atipamezole should be used only at low doses to reverse a combination anesthesia induced by barbiturates and medetomidine.

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Atipamezole, an α_2-adrenoceptor antagonist, is more specific in binding to α_2-receptors than are the older α_2-antagonists yohimbine or idazoxan (1). However, atipamezole also interferes with serotonergic (2) and α_1-adrenergic systems (1). It reverses medetomidine-induced sedation (1), analgesia (3), and *d*-medetomidine-induced hypnosis (4) in the rat. Because humans tolerate atipamezole well (5), it has been suggested for clinical use as an antianesthetic drug (6).

In animal experiments, *d*-medetomidine enhances the effects of inhaled anesthetics (7,8) and opiates (9). Yet, *d*-medetomidine reduces opiate-induced side effects during anesthesia (10,11). *d*-Medetomidine may also be used as an anesthetic in its own right rather than as an adjunctive or supplemental drug (7). A racemic (1:1) mixture of active *d*- and inactive *l*-medetomidine used for premedication in dental surgery (12) or in human experimental pain studies (13) reduces the apprehension related to painful procedures. Moreover, *d*-medetomidine, used as premedication in minor gynecologic surgery, reduces the amount of thiopental needed for the induction of anesthesia (14).

Our study determined the relative dose of atipamezole that antagonizes the hypnotic and antinociceptive effects of medetomidine. We also studied the effects of atipamezole on methohexital-, pentobarbital-, and pentobarbital + medetomidine-induced anesthesia.

Methods

Animals

Naive male Han-Wistar rats (aged 5–6 mo, weight 410–540 g, six per cage, light 12 h-dark 12 h, lights on 6 AM to 6 PM, humidity 35%–50%, food ad libitum) were used. In the experiments presented here, the volume of injections of saline solution or atipamezole was 0.5 mL/kg, unless otherwise indicated. During the experiments, the body temperature of the rats was kept constant with heating lamps. The experiments were performed between noon and midnight.

Testing Procedures

The experimental procedures used were approved by the Ethical Committee of Animal Research of the University of Helsinki and the Provincial Government of Uusimaa, Finland.

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The animals were tested for two variables: hypnosis by means of the righting reflex and analgesia by means of a tail-pinch test. Hypnosis was determined as a state in which a rat could be placed on its back after induction of anesthesia without righting itself. The duration of this state was referred to as the duration of hypnosis (4). The duration of analgesia during anesthesia was determined with the modified pinch test, in which a standard hemostatic clamp was applied to the tail. The latency to the biting or licking of the clamp was measured (3). First, eight control rats underwent tail-pinch testing 20 min after injection of saline solution to determine the 95% confidence level for comparison with the subsequent drug-induced analgesia results. On the basis of these tests, the clamp was removed after 60 s if no response was observed. The tests were performed 20 min and once every hour after the first anesthetic injection for 5–8 h.

Experiment I

In this experiment, five groups of six animals were studied to investigate the dose and the site-related effect of atipamezole to antagonize both the hypnotic and analgesic effect of medetomidine. All five groups received medetomidine (1 mg/kg IP [1 mL/kg] [Domitor, Farmos-Group Ltd., Turku, Finland]), and each of the five groups received one of the following: subcutaneous saline solution or atipamezole (0.03, 0.1, or 0.3 mg/kg SC or 0.1 mg/kg IP) (adjusted to a volume of 0.5 mL/kg) 5 min after the injection of medetomidine. The duration of hypnosis and analgesia was then determined as described earlier.

Experiment II

To determine the effect of atipamezole pretreatment on medetomidine-induced anesthesia (as done previously with *d*-medetomidine [4]), three groups of six rats were used. Fifteen minutes before the administration of medetomidine (1.0 mg/kg IP), each of the three groups was injected intraperitoneally with atipamezole (0.1 or 0.3 mg/kg) or saline solution. The duration of hypnosis and analgesia was then determined as described earlier.

Experiment III

In the first part of this experiment, three groups of six rats were first injected subcutaneously with pentobarbital (40 mg/kg [0.67 mL/kg]) and then with atipamezole (0.3 and 1.5 mg/kg) (5,6) or saline solution (0.5 mL/kg) 5 min later. In the second part, two groups of six rats were used. Both groups simultaneously received pentobarbital (40 mg/kg IP) and medetomidine (0.3 mg/kg [1 mL/kg]) in the abdominal subcutis. To avoid possible direct chemical interaction between the injected anesthetics, medetomidine was injected subcutaneously. The groups received saline solution (0.5 mL/kg) or atipamezole (1.5 mg/kg) in the dorsal subcutis 5–10 min after injections of pentobarbital. The duration of hypnosis and analgesia were determined as described earlier.

Experiment IV

To study the effects of atipamezole on the anesthesia induced by a fast-acting barbiturate, methohexital (60 mg/kg IP [2 mL/kg]) was administered to 16 rats. Eight of the rats received atipamezole (1.5 mg/kg SC [0.3 mL/kg]), and the other eight received saline solution (0.3 mL/kg SC) 5 min after methohexital injections. The duration of hypnosis was determined as in the previous experiments.

Statistical Analysis

To compare the duration of hypnosis or response latencies to pinch at a given time point, Kruskal-Wallis analysis of variance was applied. To compare the effects of the different treatments with the effects of saline solution treatment, the two-tailed Mann-Whitney U-test was applied; $P \leq 0.05$ represented a statistically significant difference.

Results

Experiment I

The effects of medetomidine (1 mg/kg IP) on the righting reflex and on the reaction to pinch were completely antagonized if the dose of atipamezole was ≥0.1 mg/kg SC (atipamezole was administered 5 min after medetomidine) (Figures 1 and 2). However, when atipamezole was administered intraperitoneally, the reversal of the effect of medetomidine on the reaction to pinch was not as complete as with subcutaneous administration of atipamezole (Figure 2).

Although the medetomidine-induced loss of righting reflex was reversed at the dose of 0.1 mg/kg of atipamezole, the rats were sedated and immobile for the first 3–4 h of the 5-h follow-up time. Atipamezole (0.03 mg/kg) did not decrease the duration of the medetomidine-induced loss of righting significantly, but it seemed to prolong the onset of hypnosis: 10 min after medetomidine injection, three of six rats had not lost their righting reflex, whereas all rats in the medetomidine + saline solution-treated group

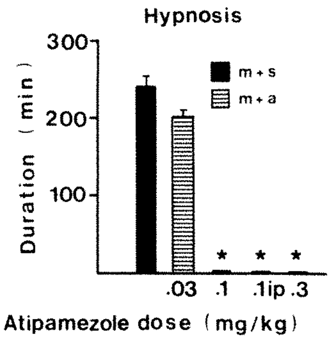

Figure 1. Effects of different doses of atipamezole on the duration of hypnosis induced by medetomidine (1 mg/kg IP). The duration of hypnosis was determined as the duration of the loss of the righting reflex. Atipamezole was injected subcutaneously 5 min after medetomidine. *Bars* show the means and *brackets* the SEM of the treatment groups. The differences between the groups are statistically significant ($P < 0.001$, f = 4, Kruskal-Wallis). *Statistically significant difference from the medetomidine + saline solution-treated rats ($P < 0.05$, Mann-Whitney). s, Saline solution; m, medetomidine; a, atipamezole.

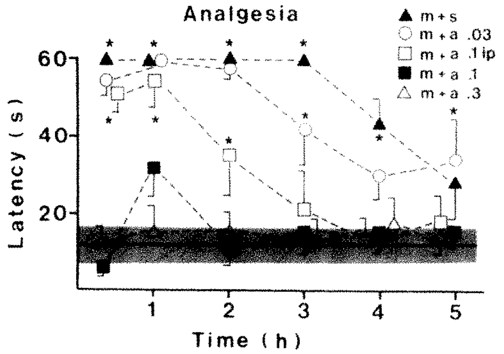

Figure 2. Effects of different doses of atipamezole on analgesia induced by medetomidine (1 mg/kg IP). The analgesic effect was determined as an increase in the biting latency to a noxious tail pinch. Atipamezole was injected subcutaneously 5 min after medetomidine. *Symbols* show the means and *brackets* the SEM in the treatment groups. A *horizontal line* shows the mean and a *shaded area* shows the ±SEM of the biting latencies in the saline solution-treated rats ($n = 8$). The groups differ from each other from 20 min to 4 h statistically significantly ($P < 0.05$, f = 5, Kruskal-Wallis). *Statistically significant difference from the response latencies in the saline solution-treated rats ($P < 0.05$, Mann-Whitney). s, Saline solution; m, medetomidine; a, atipamezole.

had lost this reflex. For the three atipamezole-treated rats, the medetomidine-induced loss of the righting reflex took 30–50 min to occur.

After the medetomidine + saline solution injections, the righting reflex of two of six of the rats was restored for a few seconds after the tail pinch at 20 min and 1 h. A motor response to the tail pinch was seen in medetomidine + saline solution-treated rats: at least a phrenic twitch was present in all animals.

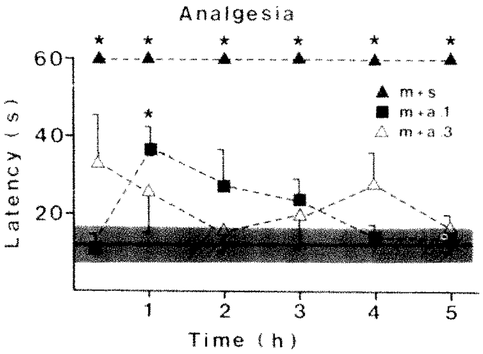

Figure 3. Effects of different doses of atipamezole on analgesia induced by medetomidine (1 mg/kg IP). Atipamezole was injected intraperitoneally 15 min before medetomidine. The groups differ from each other statistically significantly for the entire follow-up period ($P < 0.001$, f = 3, Kruskal-Wallis); symbols as in Figure 2.

Experiment II

When injected 15 min before medetomidine, doses of 0.1 and 0.3 mg/kg IP of atipamezole completely prevented the medetomidine-induced loss of righting reflex (duration 188 ± 16 min [mean ± SE]). The medetomidine-induced increase in the response time to pinching was also inhibited by atipamezole after the first hour of follow-up (Figure 3).

After the medetomidine + saline (both intraperitoneal) injections, the righting reflex of two of six of the rats was restored for a few seconds after the tail pinch at 20 min and 1 h. The phrenic motor response to the tail pinch was seen in all medetomidine + saline solution-treated rats.

Experiment III

Atipamezole (1.5 mg/kg SC) increased the duration of the pentobarbital-induced loss of the righting reflex and the pentobarbital-induced prolongation of the response latencies to the pinch (Figures 4 and 5). With a smaller dose of atipamezole (0.3 mg/kg), only the effect of pentobarbital on the pinch-response latencies was prolonged (Figure 5).

The temporary pinch-induced recovery of the righting reflex was also seen in one of the six pentobarbital-treated rats. The phrenic motor response to the tail pinch was also seen in all barbiturate-treated rats.

If medetomidine (0.3 mg/kg) was combined with pentobarbital, atipamezole (1.5 mg/kg) prolonged their effect on the righting reflex when compared with the pentobarbital + medetomidine + saline solution-treated rats (Figure 4). The effect on the pinch-induced reaction was not prolonged (Figure 5).

After treatments with pentobarbital + medetomidine + saline solution or pentobarbital + medetomi-

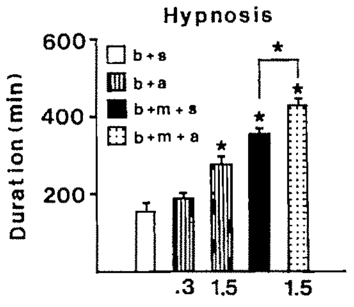

Figure 4. Effects of different doses of atipamezole on the duration of hypnosis induced by pentobarbital (40 mg/kg IP) or pentobarbital + medetomidine (0.3 mg/kg SC). Atipamezole was injected subcutaneously 5–10 min after the anesthetics. b, Pentobarbital. *Statistically significant difference from pentobarbital + saline solution-treated rats ($P < 0.05$, Mann-Whitney); other symbols as in Figure 1. The groups differ from each other statistically significantly ($P < 0.001$, f = 4, Kruskal-Wallis).

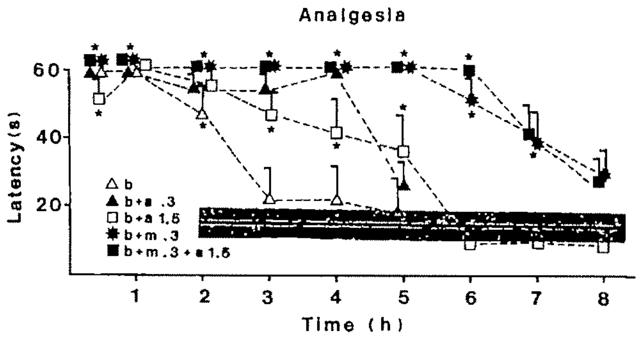

Figure 5. Effects of different doses of atipamezole on analgesia induced by pentobarbital (40 mg/kg IP) or pentobarbital + medetomidine (dose of medetomidine 0.3 mg/kg SC). Atipamezole was injected subcutaneously 5–10 min after the anesthetics. b, Pentobarbital; symbols as in Figure 2. The groups differ from each other from 20 min to 7 h statistically significantly ($P < 0.05$, f = 5, Kruskal-Wallis).

dine + atipamezole, no tail pinch-evoked motor responses were observed for the first 2 h.

Experiment IV

Methohexital-induced loss of righting reflex was also prolonged with atipamezole (1.5 mg/kg SC; 33.5 ± 6.0 min [mean ± SE]; $n = 8$) compared with the duration of metohexital + saline solution-induced hypnosis (19.6 ± 2.8 min; $n = 8$; U = 13, $P \leq 0.05$, Mann-Whitney).

Discussion

The medetomidine-induced hypnosis (i.e., the loss of righting reflex) lasted 3–4 h. This is in line with previous observations of the hypnotic effect of *d*-medetomidine: 0.5 mg/kg produced hypnosis for 3 h and 1 mg/kg for 4.5 h (4,15). When medetomidine (0.3 mg/kg) was combined with pentobarbital (40 mg/kg), the analgesic effect was more profound for the first 2 h (i.e., no motor responses could be observed), and the hypnosis lasted longer than with medetomidine or pentobarbital alone. This is consistent with previous observations in which medetomidine enhanced the effects of thiopental (14) and halothane (7,8).

Medetomidine-induced anesthesia alone is not sufficient for adequate surgical analgesia and hypnosis at the dose range used. Although response latencies to the tail pinch increased after medetomidine treatment, pinching of the tail restored the righting reflex in two of six of the rats. Furthermore, the pinch-evoked phrenic motor response was always seen if only medetomidine was used. It is not always possible to distinguish between antinociception and other reasons for delayed or missing responses to noxious stimuli by means of behavioral pain tests. Yet, there are some electrophysiologic studies that suggest that medetomidine at the dose range used in this study (16) and in *d*-medetomidine (17) produce antinociception in rats. Medetomidine (12,13) also reduces pain-evoked affective reactions. Thus, the delayed responses to the tail pinch observed in our experiments suggested that medetomidine caused mild analgesia.

The dose of atipamezole needed to restore the righting reflex during medetomidine-induced anesthesia was smaller than reported earlier. After administration of atipamezole at a dose ratio of 1:10 to that of medetomidine, the righting reflex was present regardless of whether it was injected 5 min after or 15 min before the administration of medetomidine. This corresponds to a dose ratio of 5:1 between *d*-medetomidine and atipamezole. In the study of Doze et al. (4), however, the dose ratio between *d*-medetomidine and atipamezole at which the righting reflex was not lost was 1:2 when atipamezole was injected intraperitoneally 15 min before *d*-medetomidine. Because the hypnotic effect of 1 mg/kg of medetomidine should be equal to 0.5 mg/kg of *d*-medetomidine (4,14), the difference cannot be explained by a different potency of *d*-medetomidine in the preparations used. Furthermore, Virtanen et al. (1) reported that medetomidine-induced (1 mg/kg) absence of spontaneous locomotor activity was partly inhibited by a dose of 0.3 mg/kg of atipamezole injected 30 min before medetomidine. Thus, atipamezole seems to be less effective against *d*-medetomidine alone than against the same amount of *d*-medetomidine in a racemic mixture. This may be due to an interaction between *l*-medetomidine and *d*-medetomidine or *l*-medetomidine and atipamezole.

Administration of atipamezole at a dose of 0.1 mg/kg SC reduced the medetomidine-induced increase of the response latency to tail pinching. The same dose of atipamezole injected intraperitoneally did not reverse this medetomidine-induced effect as clearly unless it was administered 15 min before medetomidine. It may be that the two solutions interact if they are injected close to each other in the same tissue within a short time. Moreover, intraperitoneal administration of atipamezole may be less effective than subcutaneous atipamezole because of high first-pass metabolism in the liver (6).

Atipamezole increased the duration of barbiturate-induced hypnosis and analgesia. This effect is opposite to that of yohimbine (18). Yohimbine shortened the duration of anesthesia that was induced with pentobarbital and xylazine, another α_2-adrenoceptor agonist (19). However, atipamezole failed to antagonize hypnosis and analgesia induced by pentobarbital and medetomidine. The mechanism of this action is unclear. Of note, atipamezole mimics the effects of pertussis toxin on *d*-medetomidine- and pentobarbital-induced anesthesia (15). Pertussis toxin, which inhibits the intracellular messenger functions of inhibitory G-proteins, decreases the hypnotic effect of *d*-medetomidine and potentiates the hypnotic effect of pentobarbital (15). Thus, atipamezole may somehow interfere with the functions of the inhibitory G-proteins.

d-Medetomidine + thiopental-induced anesthesia is already in use in clinical trials (14). Use of atipamezole in the reversal of *d*-medetomidine-induced effects in humans is undergoing clinical trials (20). In healthy human volunteers, 1.5 mg/kg of atipamezole (i.e., the highest dose of atipamezole used in this study) may cause side effects; however, these were not considered to be very unpleasant by the study subjects (6): sweating or coldness of the limbs, restlessness, tremor, increased salivation, light-headedness, or facial flush. Because atipamezole is well tolerated, it can perhaps be used as an antianesthetic drug in humans (20). In humans, the dose ratio of atipamezole to *d*-medetomidine in reversal of sedation is 40:1 (20). Because high doses of atipamezole may be needed for reversal of the effects of *d*-medetomidine in humans, the interaction between barbiturates and atipamezole should be considered when clinical experiments are planned. According to present data, high doses of atipamezole may even potentiate the effects of anesthesia induced by a combination of a barbiturate and medetomidine.

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Blood Flow and Tissue Oxygen Pressures of Liver and Pancreas in Rats: Effects of Volatile Anesthetics and of Hemorrhage

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The object of this investigation was to compare the effects of volatile anesthetics and of hemorrhage at comparable arterial blood pressures on splanchnic blood flow (radioactive microspheres) and tissue oxygenation of the liver and pancreas (surface Po_2 [Pso_2] electrodes). In contrast to earlier studies, we did not use identical minimum alveolar anesthetic concentration multiples as a reference to compare volatile anesthetics; rather, we used the splanchnic perfusion pressure. Under general anesthesia (intravenous chloralose) and controlled ventilation, 12 Sprague-Dawley rats underwent laparotomy to allow access to abdominal organs. Mean arterial pressure was decreased from 84 ± 3 mm Hg (mean ± SEM) at control to 50 mm Hg by 1.0 ± 0.1 vol% halothane, 2.2 ± 0.2 vol% enflurane, and 2.3 ± 0.1 vol% isoflurane in a randomized sequence. For hemorrhagic hypotension, blood was withdrawn gradually until a mean arterial pressure of 50 mm Hg was attained. Volatile anesthetics and hemorrhage reduced cardiac output, and hepatic arterial, portal venous, and total hepatic blood flows by comparable degrees. Mean hepatic Pso_2 decreased significantly from 30.7 ± 2.6 mm Hg at control to 17.4 ± 2 and 17.5 ± 2 mm Hg during enflurane and isoflurane (each $P < 0.05$) anesthesia, respectively. The decrease to 11.5 ± 2.5 mm Hg was more pronounced during halothane anesthesia. Hemorrhagic hypotension was associated with the lowest hepatic Pso_2 (3.4 ± 1.3 mm Hg) and the highest number of hypoxic (0–5 mm Hg 86%) and anoxic Pso_2 values (0 mm Hg 46%). Pancreatic blood flow and oxygenation remained unchanged from control during halothane and enflurane administration, whereas isoflurane increased both variables. Hemorrhagic hypotension slightly reduced pancreatic flow (−8%) but significantly decreased Pso_2 from 58 ± 5 mm Hg at control to 36 ± 3 mm Hg, with 7% of all measured values in the hypoxic range. Thus, volatile anesthetics preserved pancreatic but not hepatic blood flow and tissue oxygenation in this rat model. Despite comparable effects on perfusion, the Pso_2 of the liver and pancreas was the least during hemorrhagic hypotension compared to that with the anesthetics. Because the volative anesthetic-induced hypotension has such a different effect on splanchnic tissue oxygenation compared with hemorrhagic-induced hypotension, the authors conclude that the method of inducing hypotension may have different effects on oxygenation of various tissues.

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General anesthesia interferes with central and peripheral control of the circulation and is often associated with decreases in arterial blood pressure and cardiac output. Volatile anesthetics decrease splanchnic blood flow (1–4) and deteriorate hepatic tissue oxygenation (5,6). When the minimum alveolar anesthetic concentration (MAC) principle was applied to investigate "equipotent" concentrations of anesthetics, isoflurane had the least effect on both systemic hemodynamics and splanchnic oxygen supply, whereas halothane affected these variables the most, with enflurane intermediate (2–4,6,7).

For deliberate hypotension, volatile anesthetics can be administered to decrease arterial blood pressure to a desired level. There is, however, little information concerning the differences among clinically used halogenated anesthetics with respect to splanchnic perfusion at reduced arterial blood pressures. Knowledge of the differential effects of these anesthetics would be of relevance not only in patients with preexisting organ dysfunction, but would also

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add to the general understanding of hepatocellular damage during inhaled anesthesia (8,9).

During all types of major surgery, splanchnic oxygen supply can be endangered by sudden blood loss. Hemorrhage curtails splanchnic perfusion (10–13) and influences oxygenation of the liver and other splanchnic organs in an unknown manner. This study was designed to evaluate the effects of the halogenated anesthetics in current clinical use and of hemorrhagic hypotension on the splanchnic circulation by measuring perfusion and tissue oxygen pressures on the surfaces of the liver and pancreas at identical levels of mean arterial blood pressure.

Methods

Animals and Experimental Preparation

After approval by the local animal care committee, experiments were performed in 12 male Sprague-Dawley rats (317 ± 15 g body wt [mean ± SD]). The animals were anesthetized with chloral hydrate (40 mg/100 g body wt) intraperitoneally. Sufficient anesthetic depth was achieved throughout the experiments by intravenous infusion of α-chloralose ($2\ \mathrm{mg \cdot 100\ g^{-1} \cdot h^{-1}}$). This anesthetic regimen was chosen because it had provided stable hemodynamic conditions in earlier experiments (14) as well as in control animals over several hours. After tracheotomy, controlled ventilation with oxygen in air was provided by a small-animal ventilator through the tracheal tube. The fraction of inspired oxygen ($\mathrm{FIO_2}$) was adjusted to maintain $\mathrm{PaO_2}$ at 110–120 mm Hg. At a rate of 50–55 breaths/min, tidal volume was set to maintain $\mathrm{PaCO_2}$ at 35 mm Hg.

The animals were placed on a heating pad to maintain rectal temperature at 37°C. Polyethylene tubing was inserted into the right femoral artery for determination of arterial blood pressure and for blood gas analyses. An intravenous catheter inserted into the superior vena cava through the right external jugular vein was used for intravenous infusion of fluids and drugs. Isotonic electrolyte solution was infused at a rate of $2.5\ \mathrm{mL \cdot kg^{-1} \cdot h^{-1}}$. A polyethylene catheter was inserted into the left ventricle through the right common carotid artery. Correct position of this catheter was verified by pressure recording. Another polyethylene catheter was inserted into the tail artery for withdrawal of reference samples during microsphere injections.

Surgical Procedure

The duodenal loop segment was gently exposed together with the intramesenterically located pancreas by median upper laparotomy and placed on a Plexiglas stage. Exposed-tissue temperature was controlled by a servo feedback heating device integrated into the Plexiglas stage. The laparotomy also provided liver access. Hepatic and pancreatic surfaces were covered by a Teflon membrane to prevent drying.

Measurement of Cardiac Output and Regional Blood Flow

Blood flow to splanchnic organs and cardiac output were determined by means of radioactive microspheres (15) with the reference sample technique previously described in detail (14). We used standard carbonized microspheres with a mean diameter of 15 μm (3M Company, St. Paul, Minn.). The microspheres were suspended in hydroxyethyl starch (MW 40,000) to slow sedimentation. For each blood flow determination 120,000–150,000 microspheres suspended in 0.3 mL of hydroxyethyl starch were injected over 20 s through the left ventricular catheter, which was subsequently flushed with 0.4 mL of saline solution. An arterial reference sample was withdrawn at a rate of 0.63 mL/min. Withdrawal was started 10 s before microsphere injection and continued for 40 s thereafter (16). The rats were killed after the last microsphere injection by intravenous KCl, and the organs were removed, weighed, and placed in counting vials.

Radioactivity was determined in the following organs: liver, pancreas, stomach, small and large intestine, spleen, and right and left kidney. The number of microspheres injected was determined by subtraction of residual activity in the injection syringe from its initial value. Radioactivity of reference and organ samples was measured in a 1024-channel multiple region-of-interest gamma counter with a 3-in. crystal (model 5650, Packard Instruments, Downers Grove, Ill.). The data were corrected for background and crossover activity with a specially designed software package (17). The number of microspheres trapped and blood flow were calculated for each sample. The relatively high number of microspheres injected ensured that all probes contained a minimum of 400 spheres. Portal venous blood flow was estimated as the sum of blood flow to stomach, pancreas, small and large intestine, and spleen (18). Preportal resistance was calculated as the quotient of mean arterial blood pressure to portal vein pressure difference and total preportal flow, assuming a portal venous pressure of 10 mm Hg (19). Cardiac output was calculated from the total number of microspheres injected. Animals with nonuniform distribution of microspheres manifested by differences between left and right kidney blood flow of >10% were excluded from study.

Determination of Hepatic and Pancreatic Surface Oxygen Tension

The method used here to determine oxygen pressure fields on liver and pancreas has been described in detail elsewhere (20,21) and has proved useful in a variety of studies (6,22–24). In brief, the measuring device consists of a Clark-type electrode incorporating eight thin platinum cathodes and one Ag/AgCl anode. At a constant polarization voltage of −700 mV, a single platinum wire (diameter 15 μm) registers a reduction current linearly dependent on the partial pressure of oxygen (Po_2). The radius of the oxygen-sensitive surface area of the wires depends on the thickness of the membrane used and is 20–25 μm with a membrane 25 μm thick. Electrodes were calibrated in physiologic saline solutions equilibrated with pure nitrogen and 5% and 10% oxygen in nitrogen, before and after each measurement. Reduction current was found to be linear within this range.

We also examined potential interference by the volatile anesthetics with electrode signals by equilibrating calibration media with different concentrations of the anesthetics (0–2 vol%). No impact on electrode signals was detected with isoflurane and enflurane, whereas halothane was reduced by the electrode, leading to an increased reduction current, as reported elsewhere (25). This increase was independent of the oxygen concentration in the gas, but depended linearly on the halothane concentration; 0.5 vol% halothane increased electrode readings by 3 mm Hg, 1 vol% by 6 mm Hg, and 1.5 vol% by 9 mm Hg. Correction of the data obtained during application of halothane was not performed, because tissue concentrations of halothane were not measured.

Reduction current signals from each of the eight channels were amplified, digitized, and processed with a PDP 11/23 computer (Digital Equipment Corporation, Maynard, Mass.). Histograms to describe the distribution of hepatic and pancreatic surface Po_2 (Pso_2) were constructed using Pso_2-width classes of 5 mm Hg. At each experimental step, a total of 100–120 individual oxygen pressure measurements was obtained at 12–15 different electrode locations on both the hepatic and pancreatic surfaces. The distribution of the Pso_2 values reflects average tissue oxygenation, giving the net result of nutritive blood flow, microcirculatory blood flow distribution, and tissue oxygen consumption (26). Snug contact of the electrodes with organ surfaces was verified by suffusion with 100% nitrogen or 100% oxygen. This procedure excluded diffusion of room air into the space between electrode and tissue, as well as resorption of oxygen from the ambient air by the superficially located vessels and subsequent detection by the measuring devices.

Experimental Protocol

Each protocol included a control period in which only the intravenous anesthetic was administered as well as four experimental steps with mean arterial blood pressure (MAP) decreased to 50 mm Hg by halothane, enflurane, isoflurane, or withdrawal of blood. The control recording and hypotension by volatile anesthetics were strictly randomized. When an experiment was started with hypotension by an anesthetic, MAP was adjusted to 50 mm Hg immediately after the surgical preparation had been accomplished, and measurements were started after 30 min of stable hypotension. Recordings of hemodynamics and arterial blood gas variables were obtained and hepatic and pancreatic tissue Pso_2 was measured. Hemodynamic and arterial blood gas measurements were then repeated and followed by injection of radioactive microspheres. A period of 45 min without a volatile anesthetic in the inspired gas followed. The MAP was then lowered by the next anesthetic. Control recordings were performed while no volatile anesthetic was given for another 30 min. Animals were excluded from study if after withdrawal of an anesthetic, arterial blood pressure and heart rate did not reach baseline values within a range of ±5%. Inspired concentrations of halogenated anesthetics were measured continuously (EMMA, Engström, Sweden).

The final step of each experiment was hypotension by hemorrhage, because control experiments had shown that retransfusion of blood often did not restore control values of hemodynamics and tissue Pso_2. For hemorrhagic hypotension, arterial blood was slowly withdrawn over 10 min to lower MAP to 50 mm Hg. Before the start of measurements, the animals were allowed to stabilize for at least 30 min.

Statistical Analysis

Results of hemodynamic and blood gas variables are expressed as mean ± standard error of the mean (SEM). Statistical analysis was performed with Friedman's ranked analysis of variance followed by Wilcoxon and Wilcox multiple comparisons.

The Pso_2 histograms were analyzed by their mean values as well as by the frequency of measurements in the lowest Pso_2 class (0–5 mm Hg) and by electrode readings not different from 0 mm Hg. These measur-

Table 1. Hypotension by Volatile Anesthetics and by Hemorrhage: Systemic Hemodynamics, Arterial Blood Gases, and Hemoglobin Concentrations

	Control anesthetic (IV chloralose)	Halothane	Enflurane	Isoflurane	Hemorrhage
Vol %	0	1.0 ± 0.1	2.2 ± 0.2	2.3 ± 0.1	
MAP (mm Hg)	84 ± 3	50 ± 0.2	50 ± 0.1	50 ± 0.2	50 ± 0.5
CO (mL/min)	83 ± 6	62 ± 4^a	63 ± 4^a	67 ± 3^a	61 ± 4^a
HR (min^{-1})	387 ± 7	342 ± 5^a	340 ± 6^a	350 ± 8^a	409 ± 8^b
SVR (dyne·s·cm^{-5})	99.4 ± 6.9	75.6 ± 4.2^a	74.4 ± 4.3^a	69.3 ± 3.2^a	78.5 ± 5.2^a
$R_{preport}$ (mm Hg·min·mL^{-1})	4.01 ± 0.33	3.09 ± 0.19^a	2.93 ± 0.12^a	2.8 ± 0.09^a	2.9 ± 0.2^a
$R_{hep\ art}$ (mm Hg·min·mL^{-1})	16.4 ± 2.5	16.6 ± 1.8	16.3 ± 2.1	18.3 ± 0.9	13.3 ± 1.3
SV (mL)	0.22 ± 0.02	0.18 ± 0.01	0.19 ± 0.01	0.19 ± 0.01	0.15 ± 0.01^a
Pao$_2$ (mm Hg)	119 ± 1	117 ± 1	116 ± 1	117 ± 1	116 ± 1
Paco$_2$ (mm Hg)	37 ± 1	38 ± 1	37 ± 1	37 ± 1	36 ± 1
pHa	7.37 ± 0.01	7.37 ± 0.01	7.37 ± 0.01	7.39 ± 0.01	7.39 ± 0.01
HCO$^-_3$ (mmol/L)	22.7 ± 0.3	21.3 ± 0.3	22.7 ± 0.5	22.3 ± 0.5	22.2 ± 0.3
Hb (g/100 mL)	14.1 ± 0.4	13.0 ± 0.5	14.0 ± 0.4	13.9 ± 0.3	11.6 ± 0.4^a

IV, intravenous; MAP, mean arterial blood pressure; CO, cardiac output; HR, heart rate; SVR, systemic vascular resistance; $R_{preport}$, preportal vascular resistance; $R_{hep\ art}$, hepatic arterial resistance; SV, stroke volume; Pao$_2$, Paco$_2$, arterial oxygen and carbon dioxide tensions; pHa, arterial hydrogen ion concentration; HCO$^-_3$, plasma bicarbonate; Hb, hemoglobin concentration.

Results are expressed as mean ± SEM (n = 12).

[a] $P < 0.05$ vs control.

[b] $P < 0.05$ vs control, halothane, enflurane, and isoflurane.

Table 2. Hypotension by Volatile Anesthetics and by Hemorrhage: Splanchnic and Renal Blood Flow (mL·min^{-1}·100 g^{-1})

Organ	Control anesthetic (IV chloralose)	Halothane	Enflurane	Isoflurane	Hemorrhage
Hepatic artery	53.6 ± 5.3	28.4 ± 3.4^a	28.8 ± 2.8^a	25.0 ± 1.5^a	36.2 ± 3.8^a
Portal vein	176.4 ± 12.3	120.8 ± 11.9^a	128.6 ± 4.8^a	130.2 ± 8.3^a	129.6 ± 11.5^a
Total liver	229.9 ± 15.3	149.2 ± 14^a	157.4 ± 6.8^a	155.2 ± 9.3^a	165.7 ± 12.9^a
Pancreas	66.9 ± 3.9	60.6 ± 5.2	75.1 ± 10.8	84.7 ± 9.5^a	61.8 ± 6.7
Spleen	563 ± 65	231 ± 34^a	206 ± 38^a	227 ± 29^a	167 ± 25^a
Stomach	64 ± 5	48 ± 3^{a,b}	63 ± 8	79 ± 13	50 ± 6^{a,b}
Small intestine	189 ± 15	144 ± 19	145 ± 10	135 ± 9	165 ± 16
Large intestine	97 ± 6	77 ± 4	80 ± 4	94 ± 8	70 ± 4^a
Kidneys	446 ± 22	299 ± 13^a	289 ± 22^a	287 ± 17^a	274 ± 28^a
Left kidney	446 ± 23	292 ± 15^a	349 ± 39	287 ± 20^a	265 ± 28^a
Right kidney	447 ± 20	305 ± 12^a	369 ± 42^a	288 ± 15^a	284 ± 29^a

IV, intravenous.

Data are expressed as mean ± SEM (n = 12).

[a] $P < 0.05$ vs control.

[b] $P < 0.05$ vs isoflurane.

ing points are the most relevant to assessment of critically oxygenated tissue sites. Therefore, the total number of measurements in these classes was analyzed by χ^2 test. A P value <0.05 was considered statistically significant.

Results

Changes of systemic hemodynamic variables, arterial blood gases, and hemoglobin concentrations are summarized in Table 1. Splanchnic blood flow and distribution of cardiac output are given in Tables 2 and 3, respectively. Values of hepatic and pancreatic Pso$_2$ measurements are presented in Table 4 and in Figures 1 and 2.

Systemic Hemodynamic Variables

Control MAP was 84 ± 3 mm Hg. Decreases in MAP to 50 mm Hg required inspiratory concentrations of 1.0 ± 0.1 vol% halothane, 2.2 ± 0.2 vol% enflurane, and 2.3 ± 0.1 vol% isoflurane, respectively. Control heart rate (387 ± 7 beats/min) decreased significantly by 12% during halothane and enflurane anesthesia and by 10% during isoflurane anesthesia. Cardiac output decreased during halothane and enflurane

Table 3. Hypotension by Volatile Anesthetics and by Hemorrhage: Splanchnic Blood Flow (% of Cardiac Output)

Organ	Control anesthetic (IV chloralose)	Halothane	Enflurane	Isoflurane	Hemorrhage
Total liver	31.2 ± 2.5	28.9 ± 3.5	29.6 ± 2.8	25.3 ± 1.6	30.5 ± 2.2
Hepatic artery	7.5 ± 1.0	5.4 ± 1.0	5.1 ± 0.8	4.3 ± 0.3	6.3 ± 0.5
Portal vein	23.7 ± 1.7	23.5 ± 2.7	24.5 ± 2.2	21.03 ± 1.4	24.2 ± 2.3
Pancreas	1.04 ± 0.11	1.08 ± 0.11	1.58 ± 0.38[a]	1.38 ± 0.19[a]	1.19 ± 0.11

IV, intravenous.
Data are expressed as mean ± SEM ($n = 12$).
[a] $P < 0.05$ vs control.

Table 4. Hypotension by Volatile Anesthetics and by Hemorrhage: Tissue Pso_2 of Liver and Pancreas

Tissue Pso_2	Control anesthetic (IV chloralose)	Halothane	Enflurane	Isoflurane	Hemorrhage
Hepatic Pso_2					
Mean (mm Hg)	30.7 ± 2.6	11.5 ± 2.5[a]	17.4 ± 2[b]	17.5 ± 2[b]	3.4 ± 1.3[c]
0–5 mm Hg (%)	1	29[a]	13[b]	9[b]	86[c]
0 mm Hg (%)	0	9[a]	4[b]	2[b]	46[c]
Pancreatic Pso_2					
Mean (mm Hg)	57.8 ± 5.3	64.9 ± 7.9	60.2 ± 7	70.5 ± 4.9	35.8 ± 2.7[c]
0–5 mm Hg (%)	0	0	0	0	7[c]
0 mm Hg (%)	0	0	0	0	2[c]

Pso_2, surface tissue Po_2; IV, intravenous.
Data are expressed as mean ± SEM ($n = 12$).
[a] $P < 0.05$ vs control.
[b] $P < 0.05$ vs halothane and control.
[c] $P < 0.05$ vs control, halothane, enflurane, and isoflurane.

anesthesia by approximately 25% and to a lesser extent during isoflurane anesthesia (−19%). The better preservation of cardiac output during isoflurane anesthesia was largely due to a more pronounced decrease in systemic vascular resistance (−30%) compared with halothane and enflurane (−25%) anesthesia. Control left ventricular stroke volume was 0.22 ± 0.03 mL. Hypotension induced by either of the volatile anesthetics significantly reduced stroke volume by a comparable degree (−15%).

For hemorrhagic hypotension to MAP 50 mm Hg, 5.1 ± 0.7 mL of blood (i.e., 21% ± 3%) of the estimated circulating blood volume had to be withdrawn. Hemorrhagic hypotension decreased hemoglobin concentration (−22%). Heart rate significantly increased to 409 ± 8 beats/min, and cardiac output decreased by 27%. Thus, stroke volume significantly decreased by 32% to 0.15 ± 0.02 mL/min. Systemic vascular resistance decreased by 21%. Arterial blood gases, pHa, and bicarbonate remained in the control range throughout the experiments.

Splanchnic Blood Flow

During control administration, the liver was supplied by 7.5% ± 1% of cardiac output via the hepatic artery and by 23.7% ± 1.7% of cardiac output via the portal vein (Table 3). Hypotension by volatile anesthetics and hemorrhage decreased total hepatic blood flow by decreases in both arterial and portal venous inflow. Hepatic arterial blood flow decreased comparably by 47%, 46%, and 53% with halothane, enflurane, and isoflurane, respectively, and slightly less due to hemorrhage (−32%). Portal venous flow decreased to a comparable extent independently of the anesthetic used to produce the hypotension. Percent of cardiac output distributed to the liver decreased with volatile anesthetics but was unchanged from control during hemorrhagic hypotension. Within the preportal bed, except for the pancreatic gland, all organs followed the behavior of portal flow: blood flow decreased, but the fraction of cardiac output distributed to these organs remained essentially unchanged.

Pancreatic blood flow was slightly reduced during halothane and hemorrhagic hypotension. Enflurane and isoflurane increased pancreatic blood flow compared with control (+12%, NS; +27%, $P < 0.05$). The fraction of cardiac output received by the pancreas was slightly >1% during control and halothane administration and increased significantly to 1.58% and 1.38% during enflurane and isoflurane administration, respectively. Hemorrhagic hypotension increased this fraction slightly to 1.2%.

Left and right renal blood flow values in each

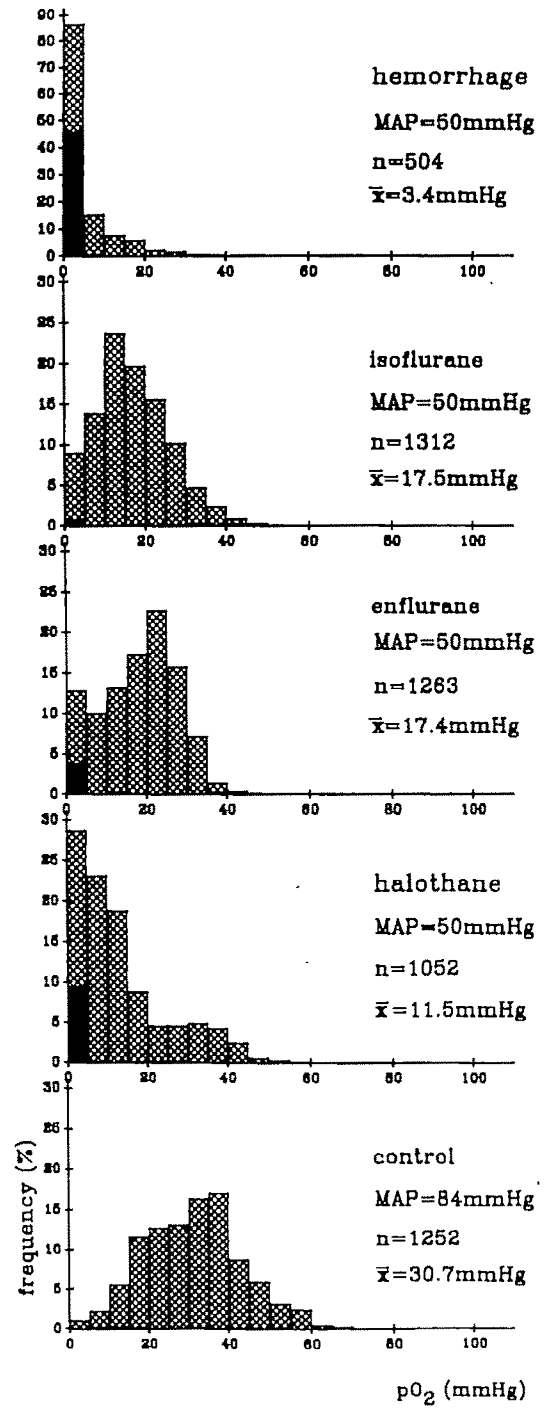

Figure 1. Summary hepatic Pso$_2$ distribution curves. The following experimental steps are given: control (MAP 84 ± 3 mm Hg); hypotension by halothane, enflurane, isoflurane, and hemorrhage (MAP 50 mm Hg). A significant leftward shift of the distribution curves (i.e., to lower mean values) and an increased number of low Pso$_2$ values were observed during hypotension. These changes were most pronounced during hemorrhagic hypotension, less during isoflurane and enflurane. *Solid bars*, relative numbers of measuring sites not detectably different from 0 mm Hg; *n*, total number of single measurements of each experimental condition; x̄, mean value of the summary histograms.

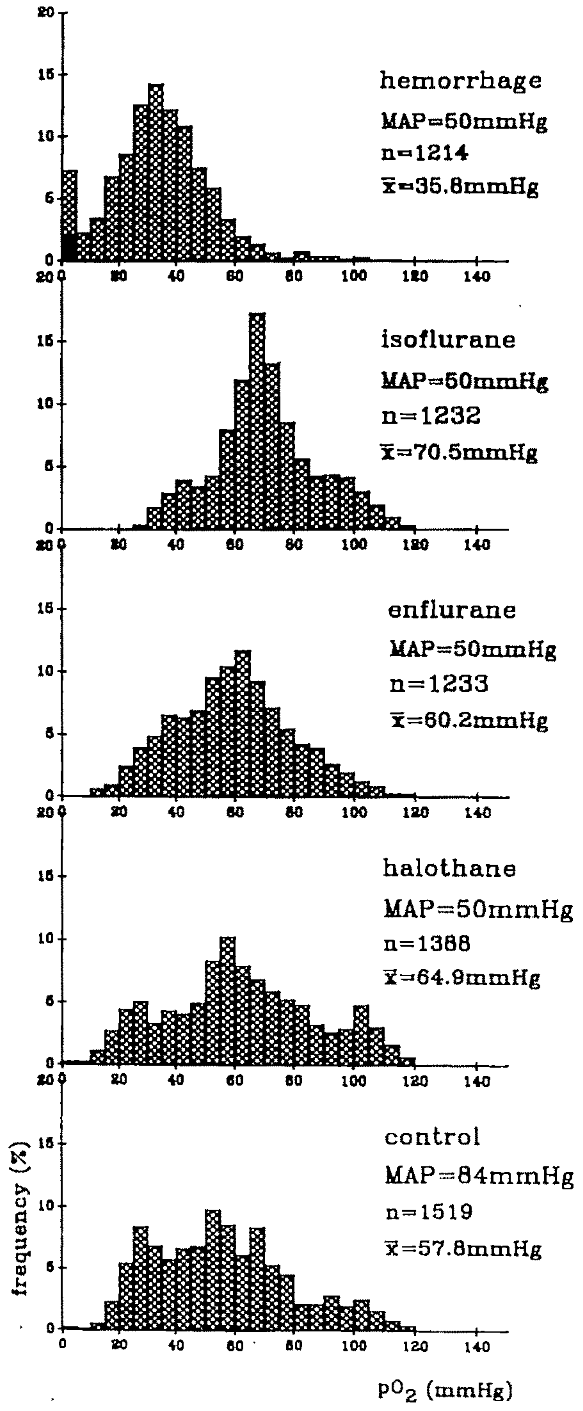

Figure 2. Summary pancreatic Pso$_2$ distribution curves. The control situation (MAP 84 ± 3 mm Hg) and the experiments with hypotension by halothane, enflurane, isoflurane, and hemorrhage (MAP 50 mm Hg) are given. No major changes of shape and mean value were detected during control and hypotension by any of the volatile anesthetics. Hemorrhage caused a leftward shift of the distribution curve and a significant increase of low Pso$_2$ values on the pancreas. *Solid bars* indicate measurements not detectably different from 0 mm Hg; *n*, total number of single measurements of each experimental condition; x̄, mean value of the summary histograms.

individual animal did not differ by >10%, indicating a homogeneous distribution of microspheres in the circulating blood.

Hepatic and Pancreatic Tissue Oxygenation

Hepatic Pso_2 histograms at control had a mean value of 31 ± 3 mm Hg, with 1% of measuring sites in the hypoxic range (0–5 mm Hg) and no readings of 0 mm Hg. During all hypotensive periods, a leftward shift of the summary histogram (i.e., to a smaller mean value) was detected (Figure 1). Despite comparable decreases in blood flow, there were marked differences in hepatic tissue Pso_2 among the volatile anesthetics and hemorrhagic hypotension. During isoflurane and enflurane anesthesia, hepatic Pso_2 decreased significantly by approximately 43%, to 17.4 and 17.5 mm Hg, respectively. Halothane caused a more pronounced leftward shift of the summary Pso_2 histogram, with the mean value reduced to 11.5 mm Hg (significantly less than enflurane and isoflurane). The frequency of Pso_2 recordings in the lowest histogram class (0–5 mm Hg) and Pso_2 recordings of 0 mm Hg amounted to 29% and 9% during halothane, and hence was significantly increased compared with enflurane (13%, 4%) and isoflurane (9%, 2%) (Table 4).

By far the lowest hepatic Pso_2 values were obtained during hemorrhage. The average Pso_2 (3.4 ± 1.3 mm Hg) was significantly different from Pso_2 values obtained during control and volatile anesthetics. Moreover, the frequency of Pso_2 values in the hypoxic range (0–5 mm Hg: 86%) was highest and significantly different from control and hypotension with volatile anesthetics (Table 4). Forty-six percent of measuring sites were not detectably different from 0 mm Hg.

The mean value of pancreatic Pso_2 was 57.8 ± 5.3 mm Hg at control, with no values in the hypoxic range (Figure 2). Administration of volatile anesthetics caused no significant changes. Mean values even increased during halothane, enflurane, and isoflurane anesthesia. The average pancreatic Pso_2 during hemorrhagic hypotension was 36 ± 3 mm Hg and hence significantly decreased from all other steps. Seven percent of the measurements were in the hypoxic Pso_2 class, and 2% were not detectably different from 0 mm Hg.

Discussion

We determined splanchnic blood flow and oxygenation of pancreatic and hepatic tissues during decreases in MAP to identical levels induced by volatile anesthetics and hemorrhage, respectively. Hypotension by anesthetics versus hypotension by hemorrhage decreased total hepatic blood flow to a comparable extent, whereas pancreatic flow was maintained. Hepatic tissue oxygen pressures decreased comparably with enflurane and isoflurane, but the decrease was more pronounced with halothane. Pancreatic oxygen pressures were slightly increased by the volatile anesthetics. Despite a comparable impact on organ perfusion, hemorrhagic hypotension impaired hepatic oxygenation considerably more than the volatile anesthetics and also decreased pancreatic oxygen pressures.

Experiments were performed in acutely instrumented and mechanically ventilated rats during constant background anesthesia. This was done to more closely reproduce the clinical situation in which volatile anesthetics are used as a tool to adjust anesthetic depth to varying intraoperative requirements or to control arterial blood pressure, or both. Earlier studies in animals have compared the effects of volatile anesthetics on the splanchnic circulation on the basis of their MAC values (3,4,6,27). The principle of MAC values implies equipotent cerebral concentrations, but disregards differing hemodynamic impact of the anesthetics. Thus, it appears difficult to differentiate the specific effects of the anesthetics on the splanchnic circulation from secondary consequences due to unspecific cardiocirculatory depression. In this study, we therefore compared anesthetic effects on the splanchnic vascular bed at the same arterial blood pressures.

The use of an anesthetized preparation reduced stress-induced disturbances of hemodynamic variables during sampling of control values. A further advantage was that the well-described negative effects on splanchnic circulation caused by onset of artificial ventilation were excluded. Controlled ventilation was also enabled not only during application of the volatile anesthetics, but also during the control period, thus avoiding the sequelae of alveolar hypoventilation by volatile anesthetics (i.e., hypoxemia and hypercapnia).

Certainly, the results of this study were not solely due to the effects of the volatile anesthetics or of hemorrhagic hypotension, because our anesthesia included separate drugs given for induction and maintenance of anesthesia (α-chloralose). As chloralose has minimal effects on gastrointestinal blood flow in small animals (28), we assumed that the effects of chloralose were small. This is supported by systemic hemodynamic and regional blood flow values similar to those obtained in conscious rats (16,29,30). Further, our anesthetic regimen was identical in all animals, and our experimental sequence—except for hemorrhage—was strictly randomized, thus minimizing influences of either baseline anesthesia or time on the results.

The intravenous anesthetic undoubtedly reduced the MAC values of the volatile anesthetics. The degree of reduction should be comparable, because chloralose was infused at an unchanged rate throughout the experiments, providing constant depth of background anesthesia. The inspired concentrations of the anesthetics probably closely resembled their end-expiratory concentrations, because each step was started with a high initial concentration of the anesthetic to achieve short equilibration periods. Accordingly, concentrations necessary to decrease MAP to 50 mm Hg would correspond to approximately 0.8 MAC halothane, 1.0 MAC enflurane, and 1.6 MAC isoflurane for unpremedicated rats (31). The differing MAC multiples applied in this study explain the apparent discrepancy with results of earlier studies in which isoflurane was found to preserve splanchnic flow better than equianesthetic concentrations of halothane or enflurane (4,6).

The technique of measuring surface tissue oxygen pressures by multichannel Clark-type electrodes has proved useful in a variety of studies (5,6,23,24). The measuring device permits atraumatic measurement of local tissue oxygenation. The hemispheric catchment area of a single wire of the electrode produces an averaged oxygen tension measurement from a tissue volume including several parenchymal cells and intravascular and interstitial space. The results of these Pso_2 measurements reflect local tissue oxygenation, giving the net result of oxygen delivery, microcirculatory blood flow distribution, and oxygen demand of the tissue. The Pso_2 measurements on organ surfaces do not necessarily reflect oxygen tensions in deeper layers of tissue. Because neither a hepatic nor pancreatic transmural oxygen gradient has been previously described, Pso_2 measurements can be assumed to describe whole-organ oxygenation.

The Pso_2 recordings not detectably different from 0 mm Hg do not necessarily indicate that intracellular Po_2 or cellular oxygen availability is in fact zero because of the poor resolution of the device in this range; however, we stress that these low values must be taken into consideration when evaluating the quality of tissue oxygenation. Statistical analysis was therefore performed not only with average Pso_2 values, but also with Pso_2 values in the lowest histogram class (0–5 mm Hg) and with values not detectably different from 0 mm Hg.

Hepatic Blood Flow and Oxygenation

In accordance with data on splanchnic blood flow of conscious rats (16,29,30), 76% of total hepatic blood flow in our study was provided by portal venous inflow (176 ± 12 $mL \cdot min^{-1} \cdot 100\ g^{-1}$) and 24% by the hepatic artery (54 ± 5 $mL \cdot min^{-1} \cdot 100\ g^{-1}$). Tissue oxygenation not only depends on the total amount of oxygen delivered, but also on local metabolic demands and microcirculatory blood flow distribution. The combination of these factors now yielded average tissue oxygen pressures of 31 mm Hg at control conditions. These data are in general agreement with results from the literature, although obtained in different animal species (i.e., piglets [32,33], pigs [5,6]) and under varying anesthetic protocols.

Comparison of the volatile anesthetics revealed that there were no profound differences with respect to blood flow and hepatic oxygenation. Total hepatic blood flow values with the highest flow during isoflurane anesthesia and the lowest during halothane anesthesia reflect the vasodilatory properties of these substances and agree with earlier investigations (4,19), although the differences did not reach statistical significance.

In contrast, despite comparable portal venous and hepatic arterial blood flow values, distinct differences with regard to hepatic tissue Pso_2 values were observed when we compared hypotension due to anesthetics versus hemorrhage. Hemorrhagic hypotension led to a dramatic decrease in tissue Pso_2. A high percentage of tissue sites measured below 5 mm Hg indicated tissue hypoxia (20). In contrast, the volatile anesthetics only mildly affected tissue Pso_2. Marked differences in organ oxygen consumption during hemorrhagic hypotension versus identical hypotension by volatile anesthetics would account for this discrepancy. Current evidence suggests no reduction of oxygen consumption in splanchnic organs during administration of volatile anesthetics (3,7), whereas hemorrhage decreases hepatic oxygen consumption in rats (32,33). As data of hepatic venous blood gases are not available in this study, alterations in metabolic demand and oxygen consumption cannot fully be excluded. Reduced splanchnic and hepatic oxygen availability due to a decrease in cardiac output and hemoglobin content, as well as inhomogeneous distribution of capillary perfusion, would contribute most to the significant deterioration of hepatic Pso_2 during hemorrhagic hypotension versus hypotension by volatile anesthetics (20,34–36).

Pancreatic Blood Flow and Oxygenation

In the present study, control pancreatic blood flow was 80 $mL \cdot min^{-1} \cdot 100\ g^{-1}$, representing approximately 1.7% of cardiac output, which accords with results obtained in conscious rats with use of microspheres (16,29,30). We had not expected to find that pancreatic blood flow decreased only slightly (halothane, hemorrhage) or increased beyond control values (enflurane, isoflurane) at a MAP of 50 mm Hg. An earlier study in rats from this laboratory (37) revealed that at graded reductions of MAP by enflurane anesthesia to 50 mm Hg and further to 30 mm Hg, pancreatic blood flow was also maintained, whereas pancreatic vascular resistance progressively decreased. The new inhaled anesthetic sevoflurane preserved pancreatic flow in a similar rat model (14). Choice of animal species and our experimental protocol could have affected the results because others have reported that isoflurane and sevoflurane induced decreased pancreatic perfusion in pigs and dogs from awake controls (3,38).

With regard to our results obtained during administration of volatile anesthetics, we cannot determine whether the observed maintenance of pancreatic blood flow is due to intrinsic pancreatic vascular regulatory phenomena (i.e., autoregulation) or whether it reflects anesthetic-induced vasodilation. Preservation of normal perfusion even during hemorrhagic hypotension strongly suggests a major contribution of intrinsic pancreatic regulation.

Autoregulation of blood flow is defined as the ability of an organ to maintain its blood flow even under changing perfusion pressure. Kvietys et al. (39) characterized the mechanisms involved in the regulation of blood flow and oxygenation of the totally isolated canine pancreas. They concluded that a myogenic component would contribute to pancreatic blood flow regulation because decreased perfusion pressure was associated with a decrease in organ vascular resistance. A metabolic component could not be excluded, because more oxygen was extracted when blood flow was reduced (39). Eliassen et al. (40) demonstrated in rats during papaverine-induced hypotension that pancreatic blood flow increased up to 400% of normotensive values, which indicates considerable capacity for vasodilation. During yohimbine- or propranolol-induced hypotension in rats, increased pancreatic flow was reported (41). According to findings from intravital microscopy (42), the pancreas has a high capillary reserve and vascularity, which could explain the pronounced capacity for pancreatic vascular adaptation (43). During hypotension with sodium nitroprusside at a MAP of 40 mm Hg, pancreatic blood flow increased disproportionally compared with blood flow of other splanchnic organs in dogs (44). The pancreatic vasculature is suggested to be highly reactive to vasodilatory stimuli (43). The mechanism for preservation of pancreatic flow observed in this study remains to be elucidated. Intravital microscopy might be appropriate for studying pancreatic blood flow regulation during hypotensive states.

Despite maintained blood flow, pancreatic Pso_2 was significantly less during hemorrhage compared with volatile anesthetics. Inhomogeneity of perfusion during hypovolemic states has been reported during hypovolemic hypotension. We speculate that such inhomogeneity was responsible for the altered pancreatic tissue Pso_2 also encountered in this study (20,34–36).

Thus, volatile anesthetics at a MAP of 50 mm Hg decreased total hepatic blood flow and tissue oxygen pressures to a similar extent. Isoflurane was associated with the most pronounced pancreatic vessel vasodilation and resulted in pancreatic tissue oxygen pressures higher than normal. The ultimate reason for maintenance of perfusion and oxygenation even at such a low pressure is not clear. Withdrawal of blood to a MAP of 50 mm Hg reduced splanchnic flow, as did the anesthetics. However, hemorrhage was influenced by inhomogeneity of perfusion and deteriorated hepatic and pancreatic tissue oxygen pressures more than by the anesthesia. Therefore the manner in which hypotension is induced also has a profound impact on splanchnic tissue oxygenation.

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Osmolalities of Propylene Glycol-Containing Drug Formulations for Parenteral Use. Should Propylene Glycol Be Used as a Solvent?

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Propylene glycol (PG) is a widely used vehicle for water-insoluble drugs. Injection of drugs formulated with this solvent often results in pain, thrombosis, or thrombophlebitis that can be reduced by premedication with local anesthetics or opioids. Because osmolality and pH that are unphysiologic may cause these adverse effects, we assessed the contribution of PG to the osmolality of parenteral drug formulations. Osmolality of PG measured in distilled water showed that PG content and osmolality were directly related: 2% wt/vol PG, 264 mOsm/L; 100% PG, 15,200 mOsm/L. The osmolalities of commercially available preparations of drugs dissolved in PG ranged from 365 mOsm/L (2% PG content) to 12,800 mOsm/L (83.46% PG), with most above 1000 mOsm/L. Replacement of PG by a solvent with lower osmolality in Germany has effectively reduced the incidence of side effects for one drug. Until PG can be replaced in drugs, we recommend diluting drugs in a large volume of saline solution; this may help to minimize the undesirable effects of this solvent.

(Anesth Analg 1992;75:431–5)

Pain on injection and thrombosis or thrombophlebitis after intravenous administration of various drugs are frequent, undesired side effects (1–3). Besides causing direct chemotoxic effects, the unphysiologic osmolality and pH of these drugs are mechanisms of inflammation and histologic changes in vessels (4–6) and may cause hemolysis (7). Etomidate, for example, known to be painful on injection and to frequently cause thrombophlebitis (2), has an osmolality of 4965 mOsm/L (8).

Muscle damage and increased creatinine phosphokinase activity in plasma are directly associated with both the volume and the osmolality of substances injected intramuscularly (9). Most of the irritant properties on intramuscular injection of a chlordiazepoxide preparation have been attributed to the osmolality and pH conveyed by propylene glycol (PG), the solvent in which it is prepared and administered (3). Propylene glycol is also the solvent vehicle for many other drugs that anesthesiologists administer, for example, etomidate, nitroglycerin, diazepam, lorazepam, and dexamethasone.

Although the osmolalities of many parenteral drugs often used in anesthesia have been measured, their solvents have not been listed (8). The purpose of this study was to assess the proportion contributed by the solvent PG to the overall osmolality of drug preparations. We measured the osmolality of standard solutions of PG in distilled water and the osmolality and pH of drug formulations containing PG. These values were also determined for two new preparations of etomidate, apparently devoid of venous side effects (2,10), and for propofol, known to be painful on intravenous injection (11).

Methods

Eighteen commercially available drugs for parenteral administration with PG contents ranging from 2% to 83.64% (wt/vol) were investigated. Included were an induction hypnotic, benzodiazepines, corticoids, an antibiotic, five drugs often used by anesthesiologists in emergency or intensive care settings, and diclofenac formulations for intramuscular injection. In addition to PG, 10 of these drugs contained other

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solvents or preservatives, such as benzyl alcohol, benzoic acid, ethanol, and sodium disulfite.

Etomidate in lipid emulsion (10% medium-chain triglyceride and 10% soybean emulsion, B. Braun, Melsungen, Germany) and etomidate in hydroxypropyl-β-cyclodextrin (Janssen, Neuss, Germany), two new preparations currently under clinical investigation, were supplied by the manufacturers. Stock solution of PG (Caelo, Hilden, Germany) was used. For dilution we used double-distilled water and commercially available 0.9% saline solution or glucose 5%. Three series of measurements were performed:

1. Osmolality of solutions containing 0%–100% PG dissolved in distilled water.
2. Osmolality and pH of all selected drugs after dilution, as indicated by product information. Etomidate in PG was diluted 1:2 in 0.9% saline solution.
3. Osmolality and pH of seven drugs kept in syringes over a 24-h period. Measurements were performed immediately after drawing the drug into a syringe and after 2, 4, 6, and 24 h. During the first 6 h, syringes were stored at room temperature (23°C) and thereafter in a refrigerator.

Osmolality was measured on an osmometer (Knauer Semi-micro Osmometer, Berlin, Germany) with an analogic, triple-range scale (0–400, 0–800, and 0–1600 mOsm/L). Drugs with osmolality >1600 mOsm/L were diluted 1:10 with double-distilled water using a 1000-μL Eppendorf pipette and a 10 (±0.04)-mL volumetric flask. The result was multiplied by 10. Mean osmolalities were calculated from five different measurements. The coefficient of variation in measurement with this osmometer was ±1%. Values >800 mOsm/L were rounded to the nearest 10. Values of osmolality were also calculated according to the formula of theoretical osmolality:

$$\mathrm{Osm}_{\mathrm{theor}} = \phi n C,$$

where ϕ is the osmotic coefficient ($\phi = 1$); n the number of particles into which each molecule in solution dissociates ($n = 1$); and C the concentration in moles per kilogram (12). The pH value of the drug undiluted in solution was measured using a pH meter and an electrode (WTW pH meter 521 and electrode E50, Weilheim, Germany).

Results

The values of osmolality for standard solutions of PG dissolved in water (Table 1) correspond well with those calculated. Tables 2 and 3 contain osmolality and pH measurements of drugs of interest to anesthesiologists. The graphic presentation of these data show the linear relationship between PG content and the osmolality of the drug preparation (Figure 1).

Table 1. Measured and Theoretical Osmolalities of Standard Solutions of Propylene Glycol Diluted in Distilled Water

Propylene glycol %	Propylene glycol mg/mL	Propylene glycol dissolved in distilled water (mOsm/L)	Calculated theoretical osmolality (mOsm/L)
0	0	0	—
2	20	264	263
10	100	1,440	1,314
20	200	2,570[a]	2,629
40	400	5,350[a]	5,257
60	600	8,300[a]	7,885
80	800	11,200[a]	10,514
100	—	15,200[a]	13,142

[a]Measurements were performed after a 1:10 dilution with distilled water.

Table 2. Osmolality and pH of Etomidate and of Propofol

	mOsm/L	pH
Etomidate in PG (35% vol, 362.6 mg/mL)[a]	4900	5.1
Etomidate in PG (diluted to 17.5 vol %, 181.3 mg/mL, 1:2 dilution with 0.9% NaCl)[a]	2450	5.5
Etomidate in 2-hydroxypropyl-β-cyclodextrin	307	6.4
Etomidate in lipid emulsion[a]	400	7.6
Propofol[a]	295	8.2
Propofol (1:4 dilution with glucose 5%)[a]	285	8.1

PG, propylene glycol.
[a]Commercial preparation.

The osmolalities of diclofenac preparations containing at least one additional substance (benzyl alcohol, sodium disulfite, or both, or lidocaine) were between 3150 and 6210 mOsm/L, depending on PG content (194–400 mg/mL). Osmolalities of these preparations were higher than calculated from their PG content. Glucocorticoids for intravenous administration measured were dexamethasone, 2% PG, 365 mOsm/L, and prednisolone, 15% and 20% PG, 1850 and 2970 mOsm/L, respectively.

Osmolality and pH did not change for the following drugs stored in a syringe for 24 h: etomidate, diluted etomidate, etomidate in hydroxypropyl-β-cyclodextrin, etomidate in lipid emulsion, propofol, lormetazepam, diluted lormetazepam, diazepam, and diluted diazepam.

Discussion

Osmolality is a measure of the number of solute particles dissolved in 1 L of solvent. For a given concentration, solutes with a low molecular weight,

Table 3. Osmolality and pH of Drugs Administered Parenterally

Drug	Dilution ratio and solution	Propylene glycol mg/mL	Propylene glycol mOsm/L	pH
Lormetazepam (2 mg)[a]		500	6,750	5.7
Lormetazepam (2 mg)[a]	1:2 with 5% glucose	250	3,510	5.3
Diazepam (10 mg)[a,b]		450	9,900	6.5
Diazepam (10 mg)[a,b]	1:60 with 5% glucose	7.5	485	5.1
Lorazepam (2 mg)[a,c]		834.6	12,800	8.0
Lorazepam (2 mg)[a,c]	1:2 with distilled water	417	5,700	6.5
Urapidil (50 mg)[a]		100	1,530	5.8
Urapidil (2 mg/mL)[a]	1:2.5 with saline solution	40	750	5.7
Theophyllin (150 mg)/ proxyphyllin (400 mg)		200	3,020	5.1
Nitroglycerin (50 μg)[a]		331.5	4,550	3.7
Nitroglycerin (200 μg/mL)[a]	1:5 with distilled water	66.3	1,240	4.3
Digitoxin (0.25 mg)[a,d]		415	7,600	7.2
Digitoxin[a,d]	1:3 with saline solution	138.3	1,810	—
Cotrimoxazol (80/400 mg)[a,e]		414.4	8,900	10.4
Cotrimoxazol (80/400 mg)[a,e]	1:26 with saline solution	3.08	608	9.6
Phenobarbital (200 mg)[a,f]		Not declared	13,200	10.3

[a] Commercial preparation.
[b] With benzyl alcohol, 30 mg; benzoic acid, 16 mg; sodium benzoate, 196 mg; ethanol 12.6 vol %.
[c] With benzyl alcohol, 20.9 mg; Macrogol 400, 202.5 mg.
[d] With ethanol 11 vol %.
[e] With ethanol 500 mg; benzyl alcohol, 50 mg; sodium disulfite, 5 mg.
[f] With alcohol 10 vol %.

such as PG (76.1) or ethanol (46.1), contribute considerably more to the osmolality of a drug formulation than to its weight or volume (13). Figure 1 shows that the drug itself and especially additional solvents and preservatives add to the total osmolality. The measurement of osmolality with the osmometer used had a coefficient of variation of ±1%, a negligible error rate by comparison to that for measurement after dilution and supercooling.

Propylene glycol (1,2-propanediol), a polyhydric alcohol, is a viscous, colorless liquid widely used as a solvent for water-insoluble drugs and as a preservative in parenteral, oral, and topical formulations. It is regarded as less toxic than other glycols and is harmless when taken orally, with acceptable daily oral intake estimated at 25 mg/kg (13). Propylene glycol is metabolized by hepatic alcohol and aldehyde dehydrogenases to pyruvate and lactate, which can enter gluconeogenic pathways. It does not accumulate in organ tissues, but plasma levels of PG may increase rapidly with impaired renal function (14,15).

In recent years there have been many reports about side effects with PG. Hyperosmolality, increased osmolal gap, and lactic acidosis are considered responsible for neurologic symptoms, including stupor, coma, and seizures (14–16). Cardiovascular disturbances including sinus arrhythmia (17), cardiorespiratory arrest (18), myocardial infarction, and asystole (19) have been associated with drugs containing PG. Pentobarbital anesthesia in sheep resulted in pulmonary hypertension attributed to PG (20). In rats, both PG and etomidate diluted with PG inhibited the hepatic metabolism of enflurane (21).

The most frequent adverse effects are pain on intravenous injection and thrombophlebitis (1,2). Histology after injection of a diazepam formulation containing PG and of PG alone revealed vessel dilation, interstitial edema, and polymorphonuclear leukocyte infiltration with subsequent thrombotic organization. Addition of lidocaine did not alter the inflammatory reaction (4).

In vitro studies reported hemolysis when PG had been added in various concentrations to blood samples (22); however, hemolysis has also been observed in animals (7,23) and in humans (16). Radiologists have long been aware of the detrimental effects of high osmolality contrast media on cells. Erythrocyte damage is caused by loss of intracellular fluid, leading to formation of desiccocytes, which, because of rigidity, can decrease capillary blood flow and increase pulmonary arterial pressure (23). Endothelial damage led to increased permeability in rat aortic endothelium at threshold levels of approximately 1400–1600 mOsm/L (5). Hyperosmotic solutions have triggered histamine release from human basophils in vitro (24). Finally, heparin resistance has been attributed to a protaminelike effect of PG (25).

To reduce the uncomfortable sensations for patients receiving etomidate, premedication with local anesthetics or opioids is common. Premedication,

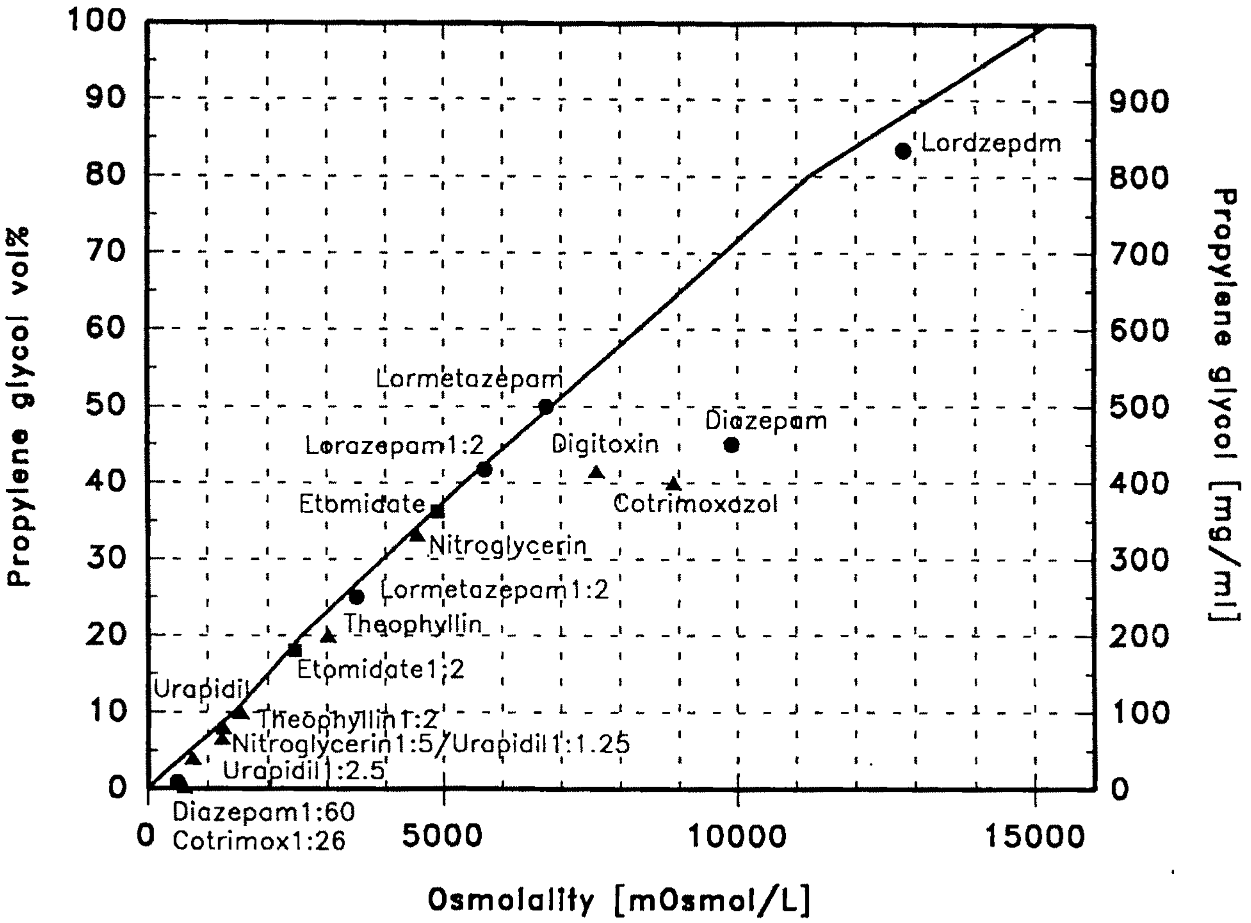

Figure 1. Propylene glycol content and osmolality of various drugs administered parenterally. *Solid line*, standard solutions of PG in distilled water; *squares*, formulations of etomidate; *circles*, the benzodiazepines; *triangles*, various drugs used in anesthesia (see Table 3).

however, does not abolish the underlying mechanism of tissue damage. Limited hemolysis and the release of mediators such as histamine are difficult to detect, and the venous sequelae that may arise during the first or second week after an operation are not always seen by an anesthesiologist.

Osmolalities of diclofenac preparations of >3000 mOsm/L cause pain on intramuscular injection and an increase in mean creatinine phosphokinase plasma activity by 120 mU/mL (3,9). Drug preparations tested that use PG as a solvent vehicle have osmolalities >1000 mOsm/L, with most >3000 mOsm/L. These values exceed those of hyperosmolar solutions that produced pain sensation in veins on the back of the hand after infusion (1.5 mL/min) or injection (1 mL/s) (6).

Diluting a drug reduces its osmolality. Osmolality is reduced by half, for example, in dilution of a drug with an equal volume of distilled water (designated 1:2); however, large volumes would have to be infused to reduce osmolality of some drugs to near plasma osmolality, 285–295 mOsm/L. Thus, necessary dilution is seldom practicable for intramuscular administration when large volumes are unacceptable. All drugs except nitroglycerin (3.7) have pH values between 4 and 11, below and above which levels pain is evoked (6).

Pharmaceutical manufacturers in the United States are not required to report the osmolalities of their drug preparations. Most package inserts of the drugs we tested listed pain and venous sequelae as possible adverse effects without giving their cause. Package inserts warned against intraarterial injection of etomidate (35% PG), lormetazepam (50% PG), and lorazepam (84% PG) because of subsequent necrosis, and mandated dilution for lorazepam and cotrimoxazol (41.4% PG).

We believe that it might be beneficial to reduce the osmolality of drug formulations to more physiologic levels and to reevaluate the use of PG in parenteral drug formulations such as nitroglycerin solutions (16). Replacement of PG in formulations of diazepam (1) and of etomidate (2,10) has successfully reduced adverse effects. Possibly, new solvents such as 2-

hydroxypropyl-β-cyclodextrin or a lipid emulsion may prove to be better alternatives.

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Sevoflurane Is Biotransformed by Guinea Pig Liver Slices but Causes Minimal Cytotoxicity

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Guinea pig liver slices were used to evaluate the biotransformation and hepatotoxic potential of sevoflurane. Precision-cut liver slices (250–300 μm thick) were incubated in sealed roller vials in buffer at 37°C under 95% O_2. Sevoflurane was added to produce 0.9 or 2.1 mM medium concentrations. After incubation (6–24 h), the intracellular K^+ content and protein synthesis were determined, along with the defluorination of sevoflurane. Isoflurane was included for comparative purposes. Sevoflurane (2.1 mM) and isoflurane (2.3 mM) had no effect on slice K^+ content, but both anesthetics depressed protein synthesis. The biotransformation of sevoflurane was maximal at 95% O_2, with threefold more F^- produced from sevoflurane than isoflurane. Sevoflurane appears to have a minimal effect on the guinea pig liver slices, which is consistent with in vivo studies in which minimal or no hepatotoxicity has been observed.

(Anesth Analg 1992;75:436–40)

Sevoflurane is a fluorinated inhaled anesthetic currently undergoing clinical trials. It provides rapid induction to and awakening from anesthesia owing to its low blood-gas partition coefficient (1). When sevoflurane was examined in rats and dogs, no toxicologic changes were seen even after frequent exposure over 2 wk; however, other preliminary studies in guinea pigs showed biochemical and histologic evidence of sevoflurane-induced hepatotoxicity (2). Additionally, when Franks et al. (3) studied the effect of volatile anesthetics on the synthesis of proteins in perfused rat livers, sevoflurane depressed the synthesis of albumin, fibrinogen, and transferrin at clinically relevant concentrations. Further studies are needed to completely understand the hepatotoxic potential of sevoflurane.

In the rat, dog, and humans, sevoflurane is biotransformed to inorganic F^- and hexafluoroisopropanol. Hexafluoroisopropanol is excreted in the urine as a glucuronide conjugate in the rat (4) and in humans (5). The glucuronide conjugate of hexafluoroisopropanol has also been detected in the bile of rats exposed to sevoflurane (6). Hexafluoroisopropanol is toxic to mice with a median lethal dose of 300–600 mg/kg (7). These investigators observed hexafluoroisopropanol to have central nervous system-depressant properties. In humans, sevoflurane appears to undergo limited biotransformation (1%–4% of the absorbed dose) and to have little or no systemic toxicity (8). No abnormalities in liver function were reported when volunteer trials were performed with sevoflurane (5,8).

The dynamic organ culture of precision-cut guinea pig liver slices is a suitable in vitro method to study the biotransformation and hepatotoxic potential of volatile anesthetics (9,10). Guinea pig liver slices can biotransform volatile anesthetics at rates comparable to those observed in vivo. Cytotoxicity of the volatile anesthetics in these liver slices can be monitored by measuring the leakage of intracellular K^+ ion from the slices and their effect on protein synthesis and secretion (10,11).

The object of this study was to determine the biotransformation and hepatotoxic potential of sevoflurane by using a sensitive in vitro system in a responding species.

Methods

The protocol for the animal studies was approved by the Animal Care and Use Committee of the University of Arizona. Adult male Hartley guinea pigs (600–650 g) are a good species and strain for studying volatile anesthetic-associated hepatic injury (12). The

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animals were obtained from Sasco, Inc. (Omaha, Neb.) and housed five animals per hanging cage on a 12-h light/dark cycle for a few days before the experiments. The guinea pigs were fed Wayne Lab Chow, cabbage, and water ad libitum.

After cervical dislocation of the animals, the liver was excised and immediately placed in cold Krebs-Henseleit buffer (4°C, pH 7.4) that contained (in grams/liter) NaCl 6.9, KCl 0.36, KH_2PO_4 0.13, $NaHCO_3$ 2.11, $MgSO_4 \cdot 7\ H_2O$ 0.29, $CaCl_2 \cdot H_2O$ 0.43, and glucose 4.5 (9,10). Cores (1 cm in diameter) were taken from different areas of the liver. Cores were sliced (25-30 mg wet wt, 250-300 μm thick) with a Krumdieck tissue slicer (13). Slices were maintained on ice in oxygenated (95%:5%, O_2/CO_2) Krebs-Henseleit buffer pH 7.4 until incubated.

Glass scintillation vials containing 1.6 mL of Krebs-Henseleit buffer (supplemented with 1.7 g/L of $NaHCO_3$, to obtain pH 7.4 at 37°C, and 1 mM each of basal medium Eagle [BME]-vitamins, BME-amino acids, *l*-glutamine, and 50 μg/mL gentamycin) were used for incubation. Three slices were incubated together on stainless steel mesh cylinders circumscribed with two wheels. Vials were usually gassed with 95% O_2/5% CO_2 except in the biotransformation studies, where the O_2 was varied between 2.5% and 95%. After 1-h preincubation, the volatile anesthetics were administered by injection through a Teflon septa cap onto a circular filter paper wick (diameter 2.2 cm). Hexafluoroisopropanol was delivered directly to the incubation medium. Vials were placed on a heated (37°C) vial rotator, housed in an acrylic plastic box, and rotated at 3.5 rpm for up to 24 h. Slices were removed after 6, 12, and 24 h and used for measuring K^+ levels, DNA content, and protein synthesis. In separate exposures, the slices and medium were collected together and used for measuring metabolites.

Aliquots of the incubating medium were extracted with *n*-heptane and the extract assayed for sevoflurane and isoflurane by gas chromatography (14). Sevoflurane or isoflurane (0.5-4 mM) in *n*-heptane was used for preparing a standard curve.

The F^- concentrations were measured with an ion-selective electrode (Onion Research, Cambridge, Mass.). Standard F^- solutions with sodium fluoride (1-2 mM) were prepared and carried through the same procedure as the sample (9); F^- production is expressed as picomoles F^- per milligram slice weight.

Slices for K^+ and DNA analysis were blotted and placed in 1 mL of deionized water and homogenized. The K^+ content was measured by flame photometry, and the DNA content of the slice was measured by a fluorometer assay and used to normalize K^+ values (10). For the analysis of protein synthesis, slices were incubated in the presence of 0.3 μCi [^{3}H]leucine per milliliter medium, blotted, homogenized in 1 mL ice-cold 1 N KOH, and assayed for protein synthesis (11). Results were expressed as disintegrations per minute (dpm) ^{3}H incorporated per milligram protein.

Chemicals

Sevoflurane was obtained from Maruishi Pharmaceutical Co. (Osaka, Japan). Isoflurane was obtained from Anaquest (Murray Hill, N.J.). *l*-Leucine-(4,5-^{3}H) (53 μCi/mmol) was obtained from ICN Biomedicals, Inc. (Irvine, Calif.). Hexafluoroisopropanol was obtained from Sigma Chemical Company (St. Louis, Mo.). *l*-Glutamine, BME-amino acids, BME-vitamins, and gentamycin were purchased from Gibco Laboratories (Grand Island, N.Y.). All other chemicals were of analytical grade and obtained from regular commercial sources.

Experiments were repeated four to five times with slices from different animals. For each experimental condition, six slices were used. Thus, 24-30 slices were assayed for each experimental point. Values were given as mean ± SEM. Comparison of values was made with a one-tailed Student's *t*-test.

Results

As with previous anesthetic studies (9-11), liquid sevoflurane (10 and 30 μL) was injected on the filter paper wick and allowed to vaporize to produce media concentrations of 0.9 and 2.1 mM. A smaller volume of isoflurane (20 μL) produced a concentration of 2.3 mM in the medium. The difference in the concentrations of the different anesthetics is due to differences in partition coefficients. The concentration of the anesthetic was maintained throughout the incubation period. This was found to be an easy and reproducible method for delivering a constant concentration of sevoflurane in the incubation medium. It should be noted that these media concentrations exceed the concentration (0.7 mM) observed in blood during sevoflurane anesthesia (15). It is at these concentrations, however, that the following effects were seen.

Sevoflurane defluorination was dependent on the O_2 tension (Figure 1). Optimal defluorination occurred in a 95% O_2 atmosphere (720 ± 115 pmol·mg slice $wt^{-1} \cdot 6\ h^{-1}$). A 2.5% O_2 atmosphere decreased the defluorination rate to 124 ± 22 pmol·mg slice $wt^{-1} \cdot 6\ h^{-1}$. Microwave-killed slices (60 s) defluorinated sevoflurane at only 39 pmol·mg slice $wt^{-1} \cdot 6\ h^{-1}$ under 95% O_2, indicating the minimal nonenzymatic degradation of sevoflurane. After exposing the slices to 2.3 mM isoflurane, F^- production was 190 ± 15 pmol $F^- \cdot$mg slice $wt^{-1} \cdot 6\ h^{-1}$ under 95% O_2 atmosphere.

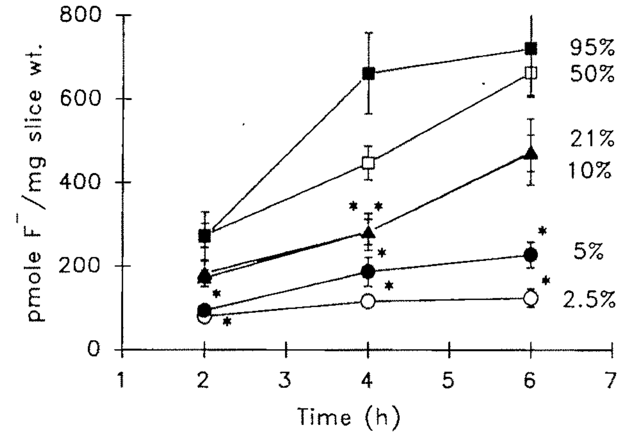

Figure 1. Defluorination of sevoflurane by guinea pig liver slices under different O_2 atmospheres. Each point represents the mean ± SEM; n = 24–30 liver slices from four to five separate animals. Sevoflurane concentration in the media was 0.9 mM. *Significant difference from value measured under 95% O_2 atmosphere ($P <$ 0.05).

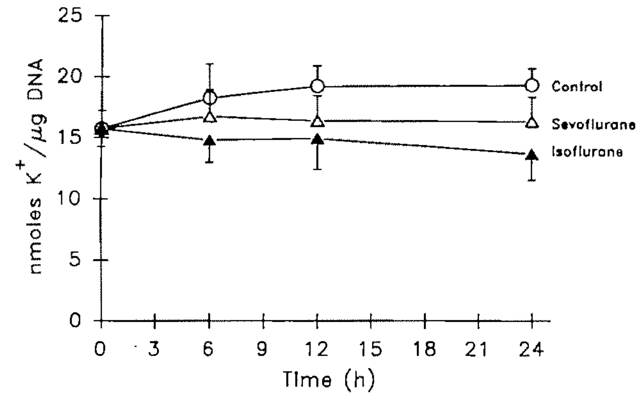

Figure 2. Effect of sevoflurane and isoflurane on guinea pig liver slice K^+ content. Liver slices were incubated with 2.1 mM sevoflurane or 2.3 mM isoflurane for 24 h in 95% O_2. Values are means of nmol $K^+/\mu g$ DNA ± SEM; n = 24–30 liver slices from four to five animals.

Guinea pig liver slices were exposed to either 2.1 mM sevoflurane or 2.3 mM isoflurane for 24 h under 95% O_2 atmosphere (Figure 2). Both sevoflurane and isoflurane had no statistical effect on the intracellular K^+ content of the liver slice, which has proved to be a reliable, early indicator of cytotoxicity (10). Both sevoflurane (2.1 mM) and isoflurane (2.3 mM) caused a significant depression (40%–50% of control) in protein synthesis in the liver slice (Figure 3) after exposure for 24 h under 95% O_2 atmosphere.

Hexafluoroisopropanol produced a time- and concentration-dependent decrease in liver slice K^+ content (Figure 4). Although 0.1 mM hexafluoroisopropanol did not alter slice K^+ content, 0.3 mM produced a linear decrease from 0 to 24 h. At a higher concentration (0.6 mM), a substantial decrease in slice K^+ content was evident by 6 h.

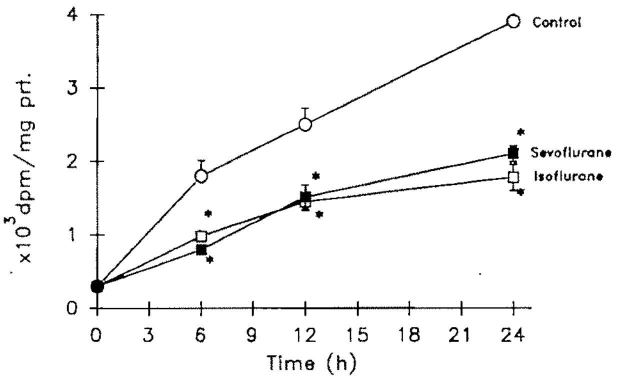

Figure 3. Effect of sevoflurane and isoflurane on protein synthesis in the guinea pig liver slices. Liver slices were exposed to 2.1 mM sevoflurane or 2.3 mM isoflurane for 24 h in 95% O_2. Values are means of disintegrations per minute (dpm) ^3H incorporated/mg protein (prt.) ± SEM; n = 24–30 liver slices from four to five animals. *Significantly different from control ($P <$ 0.05).

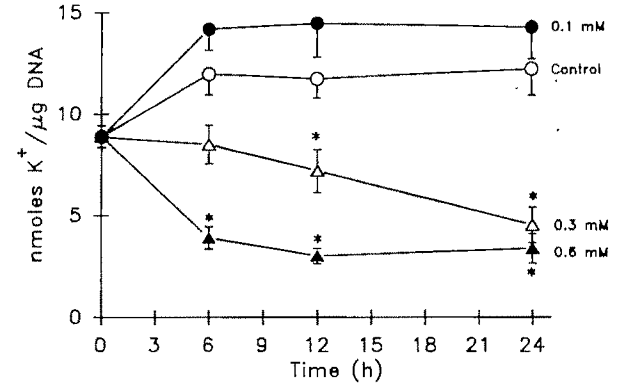

Figure 4. Effect of hexafluoroisopropanol on guinea pig liver slice K^+ content. Liver slices were exposed to three different doses of hexafluoroisopropanol under 95% O_2. Values are means ± SEM; n = 24–30 liver slices from four to five animals. *Significant differences ($P <$ 0.05) from the control value.

Discussion

The use of cultured guinea pig liver slices offers an approach that is suitable to study the biotransformation and hepatotoxic potential of volatile anesthetics (9–11,16). Although sevoflurane was readily biotransformed by the guinea pig liver slices, neither it nor the products of the biotransformation were cytotoxic to the liver slices. In addition, the primary organic metabolite, hexafluoroisopropanol, was not found to be toxic at concentrations produced by biotransformation of sevoflurane.

The rate of sevoflurane defluorination was dependent on the O_2 tension of the incubation; however, a decrease from normoxic tension (21% O_2) to hypoxic

(10% O_2) had no effect on the rate of defluorination. It is only as the O_2 tension decreased to 5% and 2.5% that the rate of defluorination was substantially decreased. Conversely, a doubling of the O_2 tension (21%–50% O_2) almost doubled the rate of defluorination. A 95% O_2 atmosphere further enhanced the rate of defluorination, but by 6 h there was no difference in the quantity of fluoride produced from slices under 95% O_2 versus 50% O_2. It should be pointed out that the O_2 tension does not absolutely reflect the dissolved O_2 in the medium nor the O_2 level throughout the slice (10). This would explain the lack of linearity at all O_2 tensions relative to sevoflurane defluorination. Overall, however, it is very evident that sevoflurane defluorination is O_2 dependent, as would be expected when one examines the products of past biotransformation studies (4–6).

Biotransformation appears to be important in producing hepatotoxicity by volatile anesthetics (12). Sevoflurane is known to be biotransformed to inorganic fluoride and to hexafluoroisopropanol (4,5). Fluoride production from sevoflurane in the guinea pig liver slices was much larger than that in the presence of isoflurane. Although sevoflurane undergoes considerable metabolism (17,18), and peak fluoride concentrations of fluoride ion approach nephrotoxic values, there has been no evidence of gross changes in renal function in either animals or humans (8,17,18).

Liver slices were used from guinea pigs because this species better resembles humans with regard to acute and mild cases of hepatic dysfunction associated with clinical halothane anesthesia (19,20). Although preliminary studies reported that sevoflurane produced a liver lesion in the guinea pig (2), the lesion was of the type produced by ischemia or hypoxia. A number of laboratories are currently examining the effect of sevoflurane on hepatic performance (21). Our liver slice system can examine the direct chemotoxic potential of sevoflurane but would not be the appropriate system to discern the effect of sevoflurane-induced hepatic ischemia or hypoxia.

Although sevoflurane and isoflurane had no effect on the intracellular K^+ content of the liver slice, both anesthetics depressed the rate of protein synthesis. Previous studies have shown that protein synthesis can be a more sensitive indicator of the early cellular alterations produced by mild toxicants such as volatile anesthetics than changes in the intracellular K^+ content of the slice (11). The depression of protein synthesis by sevoflurane in these studies confirms the work of Franks et al. (3), in which sevoflurane depressed synthesis of albumin, fibrinogen, and transferrin in the isolated perfused rat liver; however, the decrease in protein synthesis caused by sevoflurane was much less than that produced by halothane, which almost completely inhibits the process in liver slices (11).

Hexafluoroisopropanol has been reported to have central nervous system-depressant properties in mice with a median lethal dose of 300–600 mg/kg (7). The studies presented here demonstrate that hexafluoroisopropanol is cytotoxic to liver slices at concentrations of 0.3 mM and above. As there is a stoichiometric production of fluoride ion and hexafluoroisopropanol during the biotransformation of sevoflurane, blood fluoride ion levels after sevoflurane anesthesia are an indicator of the hexafluoroisopropanol produced (4,8). Blood fluoride levels are usually <30 μM; thus, an equivalent amount of hexafluoroisopropanol would be produced. Therefore it is unlikely that toxic concentrations of hexafluoroisopropanol will be produced from sevoflurane. Furthermore, hexafluoroisopropanol appears to undergo glucuronide conjugation readily, further minimizing a buildup of its concentration in either the liver or blood (6).

Overall, sevoflurane has the same effects on the guinea pig liver slices as isoflurane, which is considered the least hepatotoxic of the currently used volatile anesthetics. Although the metabolites of sevoflurane (fluoride ion and hexafluoroisopropanol) have toxic potential, they are formed in low enough quantities to not present any problems (18).

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A Cysteine-for-Arginine Substitution (R614C) in the Human Skeletal Muscle Calcium Release Channel Cosegregates With Malignant Hyperthermia

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A point mutation in the human gene for the skeletal muscle calcium release channel (ryanodine receptor [RYR1]) correlates with inheritance of malignant hyperthermia in a family of Northern European descent. The substitution of thymine for cytosine at position 1840 of the RYR1 transcript results in a cysteine-for-arginine substitution at position 614 (R614C) of the amino acid sequence. The mutation was absent in 59 normal individuals from the general population, in 61 additional unrelated malignant hyperthermia-susceptible patients, and in 18 patients with malignant hyperthermia associated with other inherited or congenital diseases. Together with reports of an equivalent mutation in six susceptible pig strains and an identical mutation in one other human pedigree, these findings suggest that the cysteine-for-arginine mutation represents a shared calcium release channel pathogenesis between porcine malignant hyperthermia and a subset of mutations responsible for the human malignant hyperthermia syndrome.

(Anesth Analg 1992;75:441–8)

Malignant hyperthermia (MH) is a pharmacogenetic myopathy elicited by widely used volatile anesthetic agents and depolarizing muscle relaxants (1). The syndrome consists of skeletal muscle rigidity, rhabdomyolysis and myoglobinuria, elevated creatine phosphokinase, hypercapnia, hyperkalemia, metabolic and respiratory acidosis, cardiac arrhythmia, and heat production. Prophylaxis and treatment with dantrolene is usually effective, although coagulopathy, renal failure, cerebral edema, coma, and death may still occur despite early detection and therapy. An estimate of the patient's perioperative risk is therefore imperative before administration of drugs capable of initiating MH.

Laboratory diagnosis of MH rests on the measurement of contracture tension generated in electrically stimulated muscle strips in the presence of halothane and caffeine. The contracture test is invasive, expensive, and time-consuming. Owing to fears of permanent disfigurement, the test is contraindicated in children weighing <20 kg, a population at substantial risk for MH. Because MH predisposition is inherited in many if not all cases, an improved method of risk assessment has been sought directly in the genetic constitution of susceptible patients. Linkage between polymorphic markers and porcine MH (2,3) facilitated assignment of the locus for halothane sensitivity to chromosome 6 of the pig (4) in a region conserved as a syntenic cluster on the proximal long arm of human chromosome 19. By virtue of its mapping to an identical position within the syntenic regions of both species (5,6), the gene encoding the skeletal muscle calcium release channel, also termed the ryanodine receptor (RYR1), became a candidate gene for the MH mutation. Altered structural and functional properties of the calcium release channel (7–9) are thought to underlie the pronounced defect in regulation of myoplasmic calcium that characterizes MH (10–12). RYR1 gates the release of calcium from the sarcoplasmic reticulum in response to the spread of depolarization from the neuromuscular junction throughout the T-tubule system. Convergent genetic and biochemical data pointing to a disorder of this protein led to the sequencing of the normal and MH pig RYR1 alleles in their entirety (13). A substitution of a thymine for a cytosine at nucleo-

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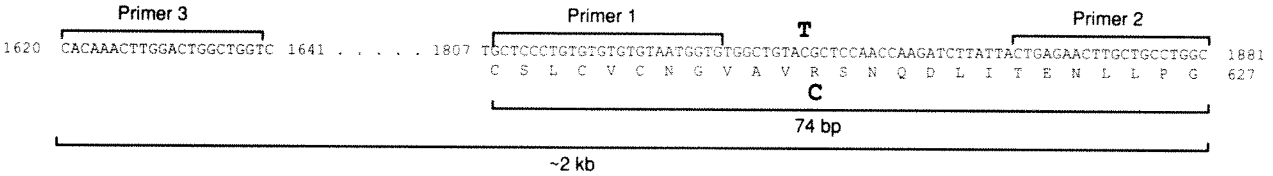
Primer 3
Primer 1
T
Primer 2
1620 CACAAACTTGGACTGGCTGGTC 1641 . . . . . 1807 TGCTCCCTGTGTGTGTGTAATGGTGTGGCTGTACGCTCCAACCAAGATCTTATTACTGAGAACTTGCTGCCTGGC 1881
C S L C V C N G V A V R S N Q D L I T E N L L P G 627
C
74 bp
~2 kb

Figure 1. A region of RYR1 DNA amplified by PCR indicating the relative positions of oligonucleotide primers 1, 2, and 3. *Numbers* refer to the nucleotide sequence of the RYR1 cDNA. *The sequence beneath primer 2* is complementary to that of the oligonucleotide used for PCR (see text). Primers 1 and 2 amplify a 74-base pair (bp) band in both genomic and cDNA. Primers 2 and 3 amplify a 2-kilobase (kb) band in genomic DNA. *Dots* interrupting the numbered cDNA sequence from 1641 to 1807 represent a region of genomic DNA containing at least two introns. Underlying the middle base of each codon is the corresponding amino acid designated by its one-letter code. The C → T nucleotide substitution and the arginine-to-cysteine amino acid substitution are highlighted.

tide 1843 was found to produce a cysteine-for-arginine substitution at position 615 in the porcine RYR1 amino acid sequence (13). The association of the RYR1 C1843 → T mutation with porcine MH has subsequently been reported in more than 450 pigs representing all six breeding strains investigated (14).

Human chromosome 19q markers within and adjacent to the RYR1 locus are tightly linked to the MH phenotype in 17 Canadian (15) and 3 Irish families (16,17). Gillard et al. (18) recently documented inheritance of a mutation equivalent to the pig substitution in 1 of 35 human MH pedigrees studied. In that family, a thymine-for-cytosine mutation at position 1840 causes a cysteine-for-arginine substitution at position 614 of the amino acid sequence (R614C). The human RYR1 C1840 → T substitution eliminates a *Rsa*I restriction endonuclease site that may be used to survey a population and to follow the mutation in a pedigree. We report a second human pedigree with cosegregation of the R614C mutation and MH, identified by screening 62 unrelated MH-susceptible subjects, 18 patients with MH associated with other inherited or congenital disorders, and 59 normal subjects.

Methods

Patients

The protocol for this study was approved by the University of Wisconsin Human Subjects Committee, and all participants gave informed consent. Patients were recruited in response to letters in scholarly journals, through meetings and newsletters of the Malignant Hyperthermia Association of the United States (MHAUS), and by referral from halothane-caffeine contracture test laboratories.

Subjects from 62 families with clinical and contracture test evidence for MH were studied: 55 families were from North America; 5 were from New Zealand, and 2 were from Iceland. When available, probands with fulminant MH events were selected for DNA analysis. Families in which the proband died during the clinical event or was otherwise not available were represented by a relative of the proband with a positive contracture test. Patients surviving events resembling MH in association with the following inherited or congenital disorders were also investigated for the concomitant presence of the R614C substitution: four with King-Denborough syndrome; two with central core disease; and one each with Duchenne's muscular dystrophy, Becker's muscular dystrophy, neurofibromatosis, tuberous sclerosis, osteogenesis imperfecta, hemorrhagic shock encephalopathy, multiple exostosis, Treacher-Collins syndrome, Turner's syndrome, Smith-Lemli-Opitz syndrome, Osler-Weber-Rendu syndrome, and Pearlman's syndrome. Fifty-nine unrelated persons from the general population with no history of neuromuscular disease were also examined. Cases from related families were excluded.

Genomic DNA Isolation

Blood samples were collected in ACD Solution A preservative (Becton Dickinson Vacutainer Systems) and shipped by overnight mail at ambient temperature. Genomic DNA was prepared from either peripheral blood lymphocytes or lymphoblastoid cell lines by nuclear isolation and lysis, protease digestion, and ethanol precipitation (19).

Polymerase Chain Reaction

Amino acid 614 in RYR1 is encoded by residues 1840–1842 in the nucleotide sequence of the mRNA. Primers were designed that closely flank nucleotide 1840 and amplify a 74-base pair (bp) fragment between nucleotides 1808 and 1881 in the mRNA of the RYR1 gene by polymerase chain reaction (PCR) (20) (Figure 1). Primer 1,5′-GCTCCCTGTGTGTGTG TAATGGTG-3′ from nucleotides 1808–1831 and primer 2,5′-GCCAGGCAGCAAGTTCTCAG-3′ complementary to nucleotides 1881–1862 of the RYR1 mRNA were synthesized by the University of Wisconsin-Madison Biotechnology Center. The PCR con-

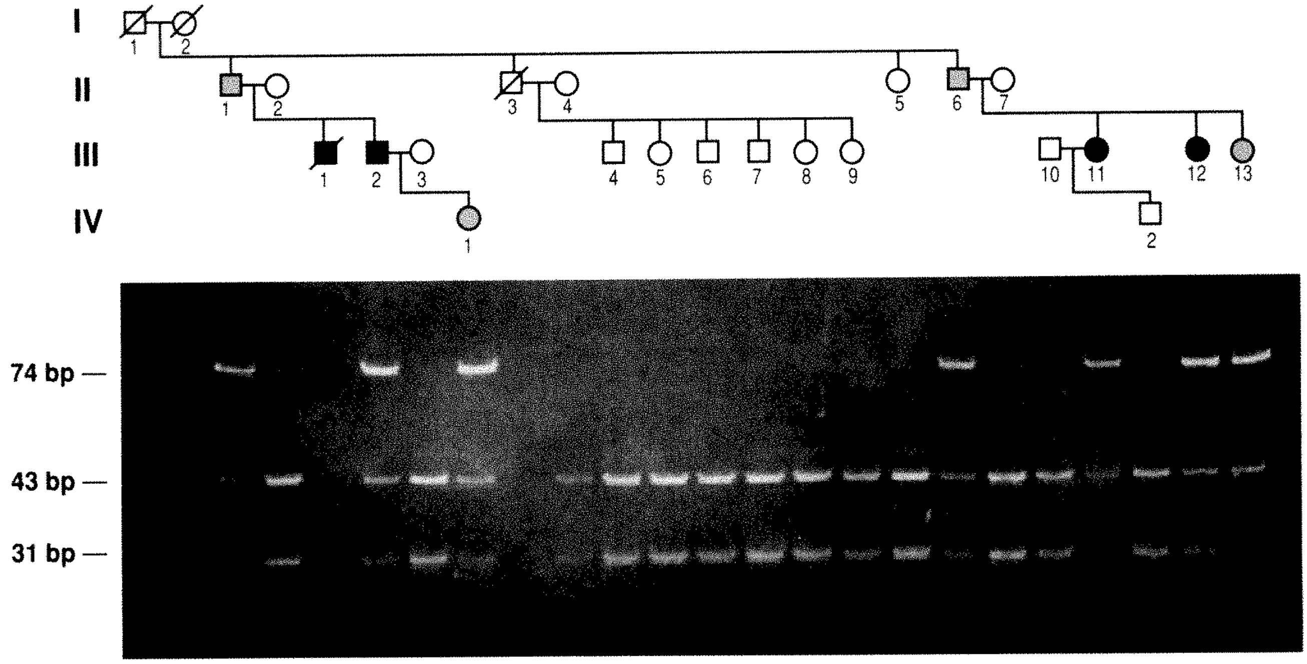

Figure 2. (**Top**) A four-generation pedigree that includes 25 persons. The proband is III-1. *Solid pedigree symbols*, MH-affected persons diagnosed by clinical event or contracture test; *shaded symbols*, persons heterozygous for the R614C mutation. (**Bottom**) Photograph of DNA fragments produced by PCR with oligonucleotide primers 1 and 2 (shown in Figure 1), followed by digestion with *Rsa*I and separation on a 20% acrylamide gel. The normal gene is identified by the presence of a cleavage site creating 43- and 31-base pair (bp) fragments. The 74-bp fragment is from the mutant allele. Thus, normal homozygotes have the site on each chromosome, with each producing two bands. The MH-affected heterozygote is distinguished by the presence of three bands; the normal chromosome produces the 43- and 31-bp bands, and the mutant chromosome produces the larger 74-bp band. *Empty lanes* are aligned beneath deceased individuals.

ditions were as follows: denaturation at 93°C for 3 min, followed by 32 cycles of denaturation at 93°C for 1 min, annealing at 54°C for 45 s, and extension at 72°C for 30 s, with a final extension step of 7 min at 72°C using a programmable thermal controller (MJ Research). The PCRs contained 500 ng of genomic DNA, 200 μM of each deoxynucleotide, 20 pmol of each primer, 50 mM KCl, 1.5 mM $MgCl_2$, 10 mM Tris-HCl pH 8.3, 0.001% gelatin, and 1.25 U of Taq DNA polymerase (Perkin-Elmer Cetus) in a total volume of 50 μL.

Primer 3,5′-CACAAACTTGGACTGGCTGGT-3′ from position 1620 to 1640 of the RYR1 mRNA was used to amplify a 2-kilobase (kb) fragment of genomic DNA when used with primer 2 (Figure 1). The PCR conditions were as follows: denaturation at 94°C for 3 min, followed by 35 cycles of denaturation at 94°C for 1 min, annealing at 64°C for 1 min, extension at 72°C for 3 min, and a final extension step of 10 min at 72°C. Other PCR conditions were as described earlier.

Detection of the RsaI *Site*

The mutation thought to be responsible for porcine MH would result in the destruction of an *Rsa*I site in the human RYR1 gene. Therefore, DNA from each subject to be tested was amplified with primers 1 and 2 (Figure 1), and half of the product was digested with 2 U of *Rsa*I (Promega) in a total volume of 40 μL for 4 h. Digested DNA was analyzed on a 20% acrylamide gel, run overnight at 8 V/cm in 45 mM Tris-Borate pH 8.3, 1 mM EDTA. Gels were stained with ethidium bromide and photographed under ultraviolet light. In samples heterozygous for the *Rsa*I site, internal controls were added to ensure that the results were not due to partial restriction digests.

Malignant Hyperthermia Diagnosis and Pedigree

Loss of the *Rsa*I recognition site was found in the brother (III-2) of the deceased proband (III-1) of the MH pedigree depicted in Figure 2. The proband's past medical history was significant only for an uncomplicated tonsillectomy with halothane, nitrous oxide, and succinylcholine anesthesia at age 5 yr. On admission, the patient was afebrile, with a normal physical examination and laboratory evaluation. He was premedicated first with prochlorperazine (10 mg IM) and pentazocine (30 mg IM), then with meperidine (75 mg IM), secobarbital (50 mg IM), and atropine (0.5 mg IM) immediately before surgery. Induction of anesthesia with sodium thiopental (300 mg IV) and succinylcholine (100 mg IV) was accompanied with "violent spastic movements" and a tight jaw, although endotracheal intubation was performed on the first attempt. Anesthetic maintenance consisted of 20% cyclopropane in 80% oxygen. Tachypnea was seen after additional succinylcholine during opening and closing of the peritoneum, and the skin was observed to be dusky and warm. At wound closure, hypotension and tachycardia preceded ventricular fibrillation, which was successfully treated with open cardiac massage, epinephrine, and sodium bicarbonate. The patient failed to regain consciousness. In retrospect it was noted that the fresh carbon dioxide absorbent was exhausted after only 40 min rather than the usual 2 h. The ensuing 24 h were characterized by hyperthermia (39.9°C), persistent myoglobinuria, arrhythmia, edematous extremities requiring fasciotomy, hyperkalemia (6.6 mEq/L), elevated creatinine phosphokinase (value not available), and metabolic acidosis. The patient died of cardiac arrest on the second postoperative day after 1.5 h of resuscitation. The autopsy showed swollen skeletal muscle fibers with obliteration of cross-striations, acute renal tubular necrosis, pulmonary congestion, and cerebral edema with signs of hypoxic injury.

The proband's family is of Northern European descent currently residing in the United States. His father (II-1) reported persistent muscle aches after anesthesia for dental extraction that included an unspecified muscle relaxant and sodium thiopental. The proband's brother (III-2) had a muscle biopsy and halothane-caffeine contracture test at age 34 yr (Hahnemann University, 1984). His history was significant for frequent muscle cramps and an episode of myoglobinuria during vigorous exercise. Muscle histology showed mild, nonspecific changes. Two muscle strips developed 2.5-g and 1.3-g contractures to 3% halothane (normal <0.7 g). The responses to caffeine were normal (0.2 g at 2 mM caffeine). Two female first cousins (III-11, III-12) also had contracture tests. They and their parents reported uncomplicated anesthetics in the past. One cousin (III-11) complained of occasional muscle cramps. Histologic investigation of her muscle showed type II muscle atrophy, with increased lipid droplets and aggregates of mitochondria on ultrastructural examination. A strip of her muscle developed 1.3-g contracture to 1% halothane (normal <0.5 g), and a normal response to caffeine (Hahnemann University, 1982). The proband's other female cousin (III-12) denied muscle cramping or other neuromuscular complaints. Two biopsy specimens from her deltoid muscle (Loyola University, 1987) generated 1.2 g and 1.4 g of tension in 3% halothane (normal <0.7 g) and 0.7 g and 0.6 g tension in 2 mM caffeine (normal <0.3 g). Muscle histology was not reported. The remainder of the family denied neuromuscular complaints, anesthetic complications, or other inherited diseases.

Digestion and Cloning

The restriction enzyme *RsaI* has a four-base recognition sequence (GTAC), and alteration of any one of these nucleotides would destroy the cleavage site. To determine whether the nucleotide substitution causing loss of the endonuclease recognition site also encodes an amino acid substitution, the region surrounding the mutation was sequenced. A 2-kb genomic DNA fragment amplified from patient III-2 with primers 2 and 3 was purified from agarose with the Magic PCR Preps DNA Purification System (Promega) digested with *Sau*3AI (Promega) and ligated into the *Bam*HI (Promega) site of the pBluescript KS+ phagemid (Stratagene). Clones containing the DNA fragment with nucleotide 1840 were identified by hybridization to ^{32}P-end-labeled primer 1. Hybridizations were performed at 45°C in 6 × SSC (SSC: 0.15 M NaCl, 15 mM sodium citrate), 1 × Denhardt's solution (0.2 g/L Ficoll, 0.2 g/L PVP, 0.2 g/L bovine serum albumin) and 0.5% sodium dodecyl sulfate overnight. The nonhybridizing probe was removed by three sequential 30-min washes at 65°C in 0.5 × SSC and 0.1% sodium dodecyl sulfate.

DNA Sequencing

The DNA was prepared from positively hybridizing colonies and sequenced by the dideoxy chain termination method (21) using double-stranded DNA as the template and a Sequenase kit (U.S. Biochemical). The DNA sequence analysis was performed using Genetics Computer Group software (22) on a VAX computer.

Results

To determine whether the R614C mutation was present in humans with MH, we amplified a 74-bp fragment of DNA containing this site. Inability of *RsaI* to cut the fragment into 43- and 31-bp fragments is indicative of a mutation in the recognition site on one of the chromosomes. In DNA heterozygous for the *RsaI* cleavage site, three products are observed after digestion: a 74-bp band representing the substituted allele and the two smaller 43- and 31-bp bands representing the normal allele (Figure 2).

We analyzed samples from 62 unrelated subjects diagnosed as MH susceptible by clinical event or contracture test, or both; 59 subjects with no previous history of MH risk; and 18 patients with intercurrent diseases who had had MH clinical episodes. Patient

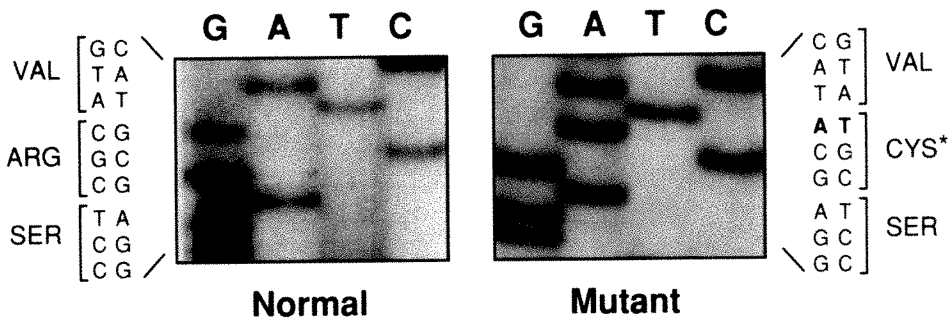

Figure 3. Autoradiogram of an RYR1 DNA sequencing gel. The sequence is from the antisense strand. The complementary sense strand is shown as is the amino acid sequence, which reads from top (amino terminus) to bottom (carboxyl terminus). The C → T substitution (*bold*) in the sense strand results in a cysteine-for-arginine substitution (*) at position 614.

III-2 (Figure 2) was the only person found to be heterozygous for the *Rsa* I site. Blood samples were obtained from this patient's close relatives, and DNA from each was analyzed for the presence of the mutation. Six additional heterozygotes were detected in three generations. No homozygotes for the alteration were found. Two of the heterozygotes (III-11, III-12) had positive contracture tests, and two (II-1, II-6) were obligate carriers. Two additional heterozygotes (IV-1, III-13) had no previous anesthetic history or contracture test but were at risk because of an affected sibling or heterozygous parent. In no instance was the presence of the substituted allele discordant with previous clinical history or laboratory investigation. All spouses tested had two copies of the normal allele. Inheritance of the MH phenotype in this pedigree on the basis of one clinical event and three positive contracture tests is compatible with a single-gene autosomal dominant mode of transmission with variable expressivity.

Subject II-3 is deceased, but six of his seven offspring (III-4 through III-9) were available for sample collection. The substituted allele was not identified in any of the six offspring or in their mother. The probability that the father had the mutation may be calculated with Baye's theorem (23) to be 1 in 31.5 (3.2%), hence it is unlikely that he inherited the mutant allele.

To confirm that the same nucleotide substitution that leads to the loss of the *Rsa*I site results in an amino acid substitution at position 614, we determined the DNA sequence from eight independent clones containing this region amplified by PCR from subject III-2. Two of the eight clones were from the substituted chromosome lacking the *Rsa*I site and with the C → T substitution at position 1840 (Figure 3). The remaining six clones from the normal chromosome had the *Rsa*I site with a C at position 1840. Therefore in this family, as in the equivalent porcine MH mutation, the C1840 → T substitution results in a substitution of a cysteine for an arginine at position 614 in the RYR1 protein.

Discussion

The major finding of this investigation is that inheritance of susceptibility to MH in 1 of 62 human pedigrees cosegregates with a substitution of cysteine for arginine in the skeletal muscle calcium release channel. The amino acid substitution arises from a C1840 → T substitution in the RYR1 gene, eliminating a recognition site for the *Rsa*I restriction enzyme. In the present family, 7 of 25 persons were heterozygous for the mutation, including three with positive contracture tests, two obligate carriers, and two persons without previous clinical history or contracture test results. Events leading to the death of the family's proband are singularly consistent with fulminant MH, and the likelihood of other clinical entities appears remote. Moreover, data from the contracture tests exceed normal cutoff points by a wide margin, supporting the correct diagnoses of the MH phenotypes in this pedigree.

The identical human mutation has recently been detected in 1 of 35 other families examined (18). The family in that report is quite small, and the clinical presentation of the proband is more indicative of masseter muscle spasm than of a convincing MH event. Furthermore, the family members were diagnosed by contracture tests that were not conducted in accord with currently accepted protocols. Under the temperature-corrected protocols used, the MH status of the proband's father was indeterminate, and the mother's results were borderline. These findings led Gillard et al. (18) to conclude that the atypical MH event and weakly positive contracture tests in their pedigree arise from a mutation that is only mildly deleterious. If the shared mutation causes MH in both families, however, little can be inferred with regard to the severity of the mutation's consequences, because in our family the event was lethal to the proband and contracture test results were well in excess of conventional normal values. Either expressivity of the R614C mutation is highly variable or differences in the details of the medical management and technical aspects of contracture testing account for the disparity. Combining data from the two investigations, 98 normal subjects failed to show the R614C mutation, suggesting that it does not exist at a high background frequency in the populations sampled and that it is unlikely that cosegregation of the mutation with MH occurs in the two families by chance alone.

Despite compelling evidence obtained by gene mapping, linkage, and mutational analysis, the causal nature of the R614C substitution in MH remains unproved. Nonetheless, abundant biochemical data support the contention that a defect intrinsic to the calcium release channel gives rise to the porcine MH phenotype. Elevations in myoplasmic calcium are observed in acute porcine MH (24) and cannot be explained by deficient activity of the calcium-adenosine triphosphatase responsible for pumping calcium from the myoplasm into the sarcoplasmic reticulum (SR) (25). Early investigations documented higher rates of calcium extrusion from porcine MH SR (10–12) through channels representing the SR constituent of the junctional triad. These channels release calcium during excitation-contraction coupling in response to T-tubule depolarization (26,27) and are modulated by calcium, magnesium, pH, adenine nucleotides (28), and acylcarnitines (29) at physiologic concentrations, as well as by a variety of pharmacologic and toxic compounds (30). Ryanodine, a plant alkaloid (31), binds to the open conformation of the channel (32), permitting the isolation and identification of the ryanodine receptor as the SR calcium release channel (RYR1) (33). Calcium release channels isolated from porcine MH muscle have an increased affinity for [^{3}H]ryanodine and an altered calcium dependency of ryanodine binding (7), defective calcium-dependent gating of single channels reconstituted in lipid bilayers (8), and distinct immunopeptide maps after digestion with trypsin (9).

In the human, Valdivia et al. (34) recently demonstrated that the MH RYR1 has a higher than normal sensitivity to calcium activation of gating and that the difference is augmented in the presence of caffeine. Hypersensitivity of the MH RYR1 to caffeine has also been found in human MH single-channel recordings (35). It is noteworthy that the calcium release channels in these investigations were isolated from persons who had not been tested for the R614C mutation or for linkage to chromosome 19 markers; hence the biochemical evidence associating human MH with altered properties of the RYR1 awaits genetic confirmation on specimens from identical sources. Despite the demonstration of biochemical abnormalities in MH tissue genotyped for the mutation, functional assays of genetically manipulated cells are required to establish the causality of the mutation. This could be achieved by expression of the normal allele transferred into phenotypically abnormal cells or by the creation of an MH-susceptible transgenic organism in a strain or species that does not exhibit MH.

The molecular events coupling sarcolemmal depolarization with changes in SR calcium permeability are poorly understood, and the manner in which a single amino acid substitution in the RYR1 molecule alters calcium gating is therefore uncertain. The RYR1 consists of 5032 amino acids with a molecular mass of 563,584 daltons (36). Approximately four-fifths of the protein comprises the cytoplasmic foot structure spanning the gap from the SR to the T-tubule sarcolemma in proximity to the dihydropyridine receptor. The functional channel is a homotetramer anchored to the SR by at least four membrane-spanning sequences at the carboxyl terminus of each molecule (36). No high-affinity calcium or nucleotide binding sites have been identified. Although glycosylation and phosphorylation sites are predicted by sequence analysis, they and the transmembrane sequences are far from amino acid 614 (36). Whether the lethal consequences of the mutation are brought forth by the loss of an essential arginine or are due to a feature of the substituted cysteine remains to be resolved. An attractive hypothesis is that the sulfhydryl group of the substituted cysteine is in an accessible and critical site for the formation of new disulfide bonds by oxidation with adjacent sulfhydryls in the MH RYR1 (37). In keeping with this premise, oxidative compounds specific for free sulfhydryl groups are known to increase SR calcium permeability, and reduction of the disulfide bonds by glutathione and other reducing agents closes the calcium release channel (38).

Even if the cysteine-for-arginine substitution is established as causal in porcine MH and a subset of human MH, important distinctions exist between the two species. Porcine MH is inherited as a recessive trait, with the homozygote manifesting the clinical episode or positive contracture test, but the mechanism of inheritance of human MH more closely fits an autosomal dominant pattern. Judging the mode of transmission in humans is not straightforward, however, because penetrance is incomplete, and expressivity is variable and dependent on exposure to an environmental factor. A difference in the apparent mode of inheritance of a trait between species does not rule out a shared molecular pathogenesis, because the identically altered gene product is expressed in a background of other gene products that may have species-specific differences under normal conditions. Variations between pigs and humans in calcium regulatory proteins other than the RYR1, such as dihydropyridine calcium channels or SR Ca^{2+}-adenosine triphosphatase, may determine whether one or two copies of a mutant RYR1 allele are required to produce the disease, as defined by the clinical event or laboratory test.

A second distinction is that all recognized porcine MH appears to derive from a common ancestor, with the cysteine-for-arginine mutation shared by all affected strains. By contrast, human MH is a much more heterogenous disorder. In humans MH has been described in families with polymorphisms linked to the RYR1 gene but without the R614C mutation (17,18) and in families in whom chromosome 19 linkage has been excluded (39). Events resembling human MH or positive contracture tests are reported in association with many other disorders, including King-Denborough syndrome (40), myotonia congentia (41), Duchenne's muscular dystrophy (42), carnitine palmitoyl transferase II deficiency (43), and central core disease. Of these, central core disease is tightly linked to the RYR1 gene (44,45), but a causative mutation has yet to be isolated. Among the many diseases that predispose to the MH syndrome in humans, only the R614C mutation appears to be shared with the disease of MH in inbred selected pig lines. Thus, the most well-studied animal analogue of MH corresponds to only a rare variant of the human syndrome. In light of this observation, the relevance of screening the potency of inhaled anesthetics, muscle relaxants, and other drugs to elicit MH in pigs before introduction into human practice must now be questioned.

We studied 18 patients with both MH and other inherited and congenital diseases. All were homozygous for the *Rsa*I recognition site at position 614 of the RYR1, underscoring the genetic heterogeneity of human MH. Many of the genes for diseases clinically associated with the human MH syndrome have been mapped to regions of the human genome not in the vicinity of the RYR1 gene. In some conditions, the association will prove to be fortuitous, with the gene carrying the MH mutation having no role in the pathogenesis of the concomitant clinical disorder. In others, the association may correspond to a single genetic defect causing both the accompanying clinical disorder and the anesthetic complication by a common pathophysiologic cascade; for example, deregulation of unbound ionized calcium in the skeletal muscle of patients with carnitine palmitoyl transferase II deficiency or Duchenne's muscular dystrophy. A mutation of any of the proteins participating in the regulation of myoplasmic calcium could potentially manifest the MH syndrome under conditions of surgical stress and anesthetic intervention.

In families in which MH-associated mutations can be identified, screening tests based on DNA analysis may be the preferred method of assigning risk. In comparison with the halothane-caffeine contracture test, mutation analysis has numerous advantages, including high efficiency and reproducibility, together with minimal cost and discomfort. Even so, clinical decision making is not trivial because the incidence of MH is unknown, and additional undetected mutations may be present. In families with identified mutations, we recommend testing all interested individuals. A positive test is evidence for MH susceptibility. Negative mutation assignment is reassuring but cannot absolutely rule out MH risk until all human MH mutations have been identified. Specific counseling with respect to risk also requires a greater understanding of the expressivity and penetrance of each mutation, as well as estimates of the new mutation rate and prevalence. Persons homozygous for the normal allele in families in which the R614C mutation is segregating are counseled to continue to avoid challenge anesthetics until these issues have been adequately addressed.

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CASE REPORTS

Radiographic Examination of Catheter Position in Restricted Sacral Block After Continuous Spinal Anesthesia

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With increasing use of microcatheters for continuous spinal anesthesia (CSA), it has been recognized that restrictive local anesthetic spread, causing prolonged sacral/perianal anesthesia and, rarely, the cauda equina syndrome, may occur (1). Although catheter malposition and drug maldistribution are likely causes of restrictive anesthetic block, such evidence in human subjects is lacking.

We report two cases of failed CSA with use of hyperbaric lidocaine, both resulting in sacrally restricted anesthesia that was significantly prolonged but completely reversible. We also present radiographic documentation of the microcatheter position, which helps to elucidate the etiology of this anesthetic complication.

Case 1

A 73-yr-old man was admitted for transurethral resection of the prostate. He had had internal fixation of a jaw fracture years earlier under general anesthesia. He had stable angina and non-insulin-dependent diabetes mellitus that was controlled by diet. His medications included metoprolol (50 mg twice daily), enteric-coated aspirin (325 mg once a day), Septra (2 tablets twice daily), and sublingual nitroglycerin (as needed). On admission, his hemoglobin was 148 g/L, and blood glucose was 13.9 mmol/L. On physical examination, there were no findings suggestive of any neurologic disease or neuropathy, and the remainder of his investigations and physical examination were normal.

With the patient in the left lateral decubitus position, a 22-gauge spinal needle was introduced at the level of the iliac crest. The cerebrospinal fluid was slightly blood tinged but cleared rapidly, with good flow. A 28-gauge spinal catheter (Medevice Inc., Mississauga, Ontario, Canada) was threaded easily to 3 cm beyond the needle tip without paresthesia. The patient was placed in a supine horizontal position, and 75 mg of lidocaine (1.5 mL of 5% lidocaine in 7.5% dextrose) (Astra Pharma, Mississauga, Canada) was injected through the catheter over 30–45 s. After 10 min, neurologic assessment revealed only sacral and scrotal anesthesia, with normal sensation and motor function in his legs. The patient was placed in 30° head-down position, but no change in sensation or motor function was noted after an additional 10 min. The procedure was abandoned, and general anesthesia was administered (propofol, fentanyl, N_2O/O_2, isoflurane). The surgery was completed 45 min later without complication. Postoperatively, while the patient was lying supine and horizontal, radiographs of the lumbar spine were taken immediately after injection of 2.0 mL of hyperbaric contrast material (Omnipaque 240, specific gravity 1.276) (Winthrop Inc., Mississauga, Ontario, Canada) through the catheter (Figure 1). In this radiograph, dye can be seen clearly within the subarachnoid space at the level of the sacrum. Perianal sensation returned to normal within 7 h, and no bowel or bladder incontinence was noted. On follow-up 1 mo later, the patient denied any subsequent bladder or bowel dysfunction.

Case 2

A 70-yr-old man was admitted for transurethral resection of the prostate. His past medical history included an inguinal hernia repair 52 yr earlier under general anesthesia and a 15-yr history of non-insulin-dependent diabetes mellitus treated with chlorpropamide (325 mg twice daily) and glucophage (1 tablet three times a day). He also had intermittent claudication on moderate exertion. He denied any symptoms suggestive of peripheral neuropathy or neurologic disease. On admission, his hemoglobin was 155 g/L, blood glucose was 29 mmol/L, and the remainder of his laboratory tests and physical examination were unremarkable. Repeat blood glucose

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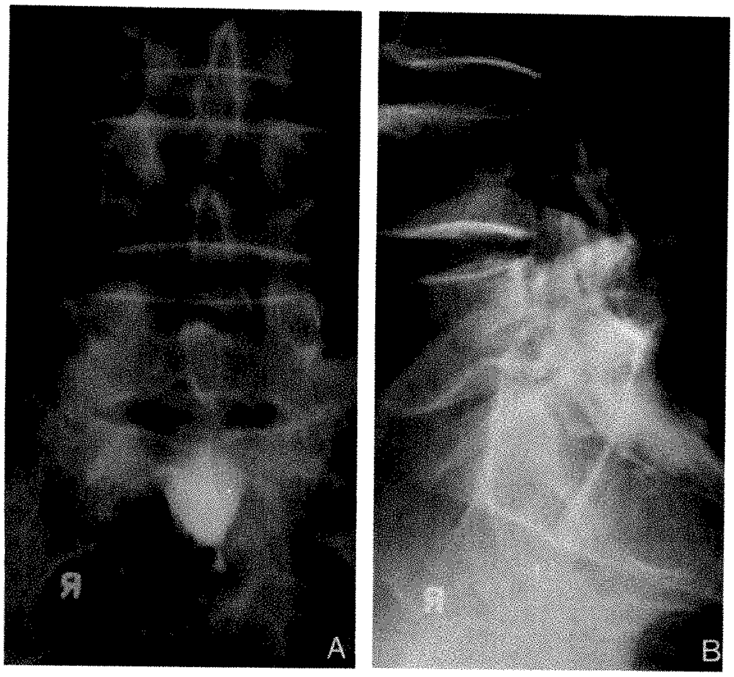

Figure 1. Anterior-posterior (**A**) and lateral (**B**) views of lumbar vertebras after injection of 2.0 mL of hyperbaric contrast material.

levels 7 h later had declined to 17.8 mmol/L after he received 6 U of subcutaneous insulin.

With the patient in the right lateral decubitus position, a 22-gauge spinal needle was inserted at the level of the iliac crest to obtain a clear flow of cerebrospinal fluid without blood or paresthesia. A 28-gauge spinal catheter was threaded easily 2–3 cm into the subarachnoid space without paresthesia. After the catheter was secured and the patient was placed in a supine horizontal position, 75 mg of hyperbaric lidocaine (1.5 mL of 5% lidocaine in 7.5% dextrose) (Astra Pharma) was injected over a 30–45-s period. After 5 min, examination revealed no sign of motor or sensory blockade in the lower extremities despite dense anesthesia in the scrotal and perianal regions. Flushing the catheter with 3.0 mL of sterile saline solution did not produce any progression in either motor or sensory anesthesia after an additional 15 min. No further doses of lidocaine were injected. The surgical procedure was then performed under general anesthesia (propofol, alfentanil, N_2O/O_2) without complication. Postoperatively, the patient continued to describe perianal and buttock anesthesia 95 min later despite continued normal motor function and sensation in his legs. While the patient was lying supine and horizontal, radiographs of the spine were taken immediately after 2 mL of hyperbaric contrast material was injected through the spinal catheter (Figure 2). In these radiographs it is evident that the dye collection lies at the level of L3-4 within the subarachnoid space. Perianal anesthesia persisted for 4 h. After removal of the bladder catheter 2 days later, the patient did not experience any bladder incontinence. Follow-up 1 mo later confirmed no bladder or bowel incontinence.

Discussion

Recent reports of cauda equina syndrome and persistent sacral root deficits after CSA are worrisome, but these neurologic complications are probably the result of direct neurotoxic damage from repeated excessive doses of local anesthetic administered in an attempt to extend a sacrally restricted block (1,2). In these unfortunate cases, the dosages of hyperbaric lidocaine and tetracaine far exceed that which would be used in a conventional single-injection technique. To avoid the development of local anesthetic neurotoxicity, Lambert and Hurley (3) suggest restricting the amount of hyperbaric 5% lidocaine to 100 mg in establishing the initial spinal block. On the basis of the favorable neurologic outcome in our two patients, we strongly recommend that this dosage guideline be followed. Despite prolonged sacral block in both patients (4 and 7 h), the neurologic deficit was reversible, and the recovery was complete.

The frequency of catheter malposition causing sacrally restricted block in CSA is currently unknown. To determine the location of radiolucent catheters in the subarachnoid space, an injection of contrast media before radiographic examination would be necessary. Iohexol dye (Omnipaque 240) has been used safely and routinely for myelographic studies. It is highly hyperbaric (specific gravity 1.276) and presumably will deposit to the most dependent region of the subarachnoid space, similar to hyperbaric

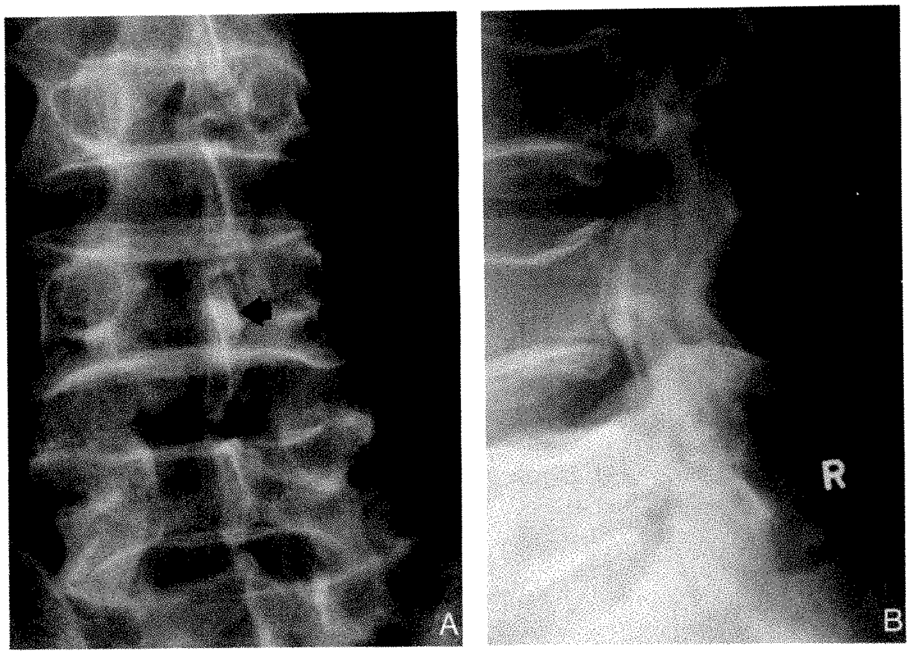

Figure 2. Anterior-posterior (**A**) and lateral (**B**) views of lumbar vertebras after injection of 2.0 mL of hyperbaric contrast material. *Arrow* indicates contrast dye collection.

lidocaine (specific gravity 1.033) but at a faster rate. Although not entirely conclusive, we believe that the dye collections seen in the anterior-posterior radiographs (Figures 1 and 2) depict the locations of the spinal catheter tips, not the gravitational pooling of the dye. In this study, radiographs taken immediately after dye injection would have kept the time of dye spreading to the absolute minimum. Furthermore, as seen in case 2, although dye and lidocaine were both injected under the same patient position condition (i.e., supine horizontal position), dye collection was found at the L3-4 level, whereas anesthetic effect was detected in the sacrum. This discrepancy in response further strengthens the notion that contrast dye was indeed highlighting the catheter tip position at the L3-4 level.

In the two cases that we have reported, although the clinical presentations are strikingly similar, the mechanism of restricted anesthetic spread in each case is distinctly different. As demonstrated radiographically, the cause of sacral anesthesia in case 1 was sacral positioning of the catheter tip. Although the insertion of the catheter was believed to be at the level of the L3-4 interspace, it is possible that the needle was introduced at the level of L4-5 and that the catheter was threaded in a caudad direction. Unfortunately, caudad deflection of the microcatheter during insertion through a straight spinal needle may occur more frequently than we realize. It is conceivable that with the use of a Sprotte spinal needle in which the lumen aperture can be oriented in a cephalad direction, or a pediatric Tuohy needle, cephalad introduction of the catheter may be enhanced. Rigler et al. (1) suggested catheter manipulation as a possible solution to correct restrictive anesthetic spread. We found that in the absence of radiographic documentation, it is impossible to determine the catheter tip position or the proper distance to pull back. Furthermore, manipulation of the catheter after stylet removal can be exceedingly difficult, owing to the small caliber and stretching of the catheter itself.

We believe that case 2 exemplifies the phenomenon of drug maldistribution in the presence of a properly placed spinal catheter. Despite the catheter tip at the L3-4 level, sacral anesthesia still occurred. This finding is in agreement with the spinal canal model data that showed that hyperbaric lidocaine preferentially pooled in the distal dependent (sacral) end of the glass tube when it was injected through a microcatheter at a level equivalent to L3-4 (3,4). In clinical practice, whether the use of a "lighter" local anesthetic solution (isobaric or hypobaric) will enhance a more uniform distribution, as demonstrated experimentally, has yet to be verified. Rigler and Drasner (4) also showed experimentally that rapid subarachnoid injection (<30 s) is another critical factor in improving distribution. Unfortunately, it is our clinical impression that manual injection of 1 mL with a tuberculin syringe through a 28-gauge catheter in <30 s is exceedingly difficult to achieve. To reach a faster injection rate (<5 s), it is necessary to use a larger caliber catheter (e.g., 20 gauge), which may still result in maldistribution and more likely a higher incidence of postdural puncture headache (5).

We were unsuccessful in promoting cephalad spread of hyperbaric lidocaine by either placing the patient in a 30° head-down position (case 1) or flushing the catheter with sterile saline solution (case 2). It is unlikely that head-down tilting after the establishment of sacral anesthesia would have a significant effect; however, this maneuver may prove beneficial before further injections. Conceptually, catheter flushing with several milliliters of saline solution may help to dilute the localized anesthetic, but we found that this maneuver still failed to promote cephalad spread.

In summary, we have presented two cases of failed continuous spinal anesthesia. Although the mechanism of restricted local anesthetic distribution in each case was distinctly different, they cannot be distinguished on clinical grounds. By limiting the maximal amount and concentration of local anesthetic used, and by accepting when the CSA has failed, it is likely that serious neurologic complications can be prevented. Future clinical studies to document the causes of CSA failure (catheter malposition versus drug maldistribution) and their frequency of occurrence would be of clinical importance.

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Patient-Controlled Spinal Analgesia for Postoperative Pain Control

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With continuous spinal anesthesia, maintaining the catheter for postoperative analgesia can be a natural extension of its intraoperative use. The use of a continuous intrathecal catheter for patient-controlled analgesia (PCA) has not been reported. We report a case of patient-controlled spinal analgesia with fentanyl.

Case Report

A 70-yr-old woman (111 kg, 157 cm) presented with a comminuted subtrochanteric fracture of the right hip. Her medical history included chronic obstructive pulmonary disease, deep venous thrombosis of both lower extremities, and peripheral vascular disease; medications included lorazepam and furosemide. The scheduled procedure was a right femoral intramedullary nailing with a Russell-Taylor Recon nail and cerclage wiring.

With the patient in the left lateral decubitus position, a 17-gauge Tuohy needle was placed at the L2-3 interspace, and a 18-gauge catheter (Perifix, Burron, Bethlehem, Pa.) was inserted 3 cm into the subarachnoid space; no paresthesias were elicited during placement. A millipore filter was connected to the catheter. The patient was turned to the supine position, and a total of 50 mg of 5% lidocaine with 7.5% glucose was injected incrementally over 15 min, resulting in a sensory blockade to T-10. The patient was then repositioned supine on a fracture table by the surgeons. Another 50 mg of lidocaine and 12.5 μg of preservative-free fentanyl was injected incrementally through the intrathecal catheter 1 h later, just before making the surgical incision. During the 4.5-h procedure, an additional 150 mg of lidocaine in divided doses was administered through the catheter to maintain a sensory blockade to T-10. The patient was maintained in the horizontal position throughout all injections and for the duration of the procedure. A total of 6 mg of midazolam and 150 μg of fentanyl was administered intravenously throughout the procedure for sedation in support of the spinal anesthetic.

The patient was moving her legs on arrival in the recovery room and complained of pain within 10 min. Her level of sensory blockade was to L-3. Analgesia was evaluated by a visual analogue scale (VAS) in which 10 cm indicated maximal pain and 0 cm complete pain relief. This patient's pain score was 10. After injection of 12.5 μg of fentanyl through the catheter, her score decreased to 5 within 15 min. A PCA pump (Pancretec, Provider 5500, San Diego, Calif.) with a reservoir of fentanyl in preservative-free normal saline solution (2 μg/mL [250 mL]) was connected to the catheter. Initial settings were for a 3-mL (6 μg) bolus dose with a lockout interval of 1.5 h. After the patient was instructed in the use of PCA, she was discharged to the stepdown unit with a VAS score of 5, feeling comfortable. Vital signs were monitored every 2 h. The VAS score and level of consciousness were documented every 8 h.

Over the next 12 h, 24 mL (48 μg) of fentanyl was used. The patient made a total of 33 requests, 8 of which were delivered. Her VAS score remained 5. The lockout interval was decreased to 1 h. During the next 24 h, 21 mL (42 μg) of fentanyl was used in seven doses (the patient made nine requests). Her VAS score ranged from 3 to 5. In the final 24-h period of catheter use, the patient's activity was increased, and she was moved to a chair twice during the day. Fentanyl (33 mL [66 μg]) was administered on 11 occasions (in response to 21 requests). Her VAS score ranged from 1 to 3. Indomethacin and oxycodone with acetaminophen were administered orally. The catheter was removed without difficulty; the tip was sent for culture, and results were negative. The patient never experienced any signs of postdural puncture headache, nausea, pruritus, respiratory depression, or somnolence. She was discharged on the seventh postoperative day, pleased with her treatment.

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Discussion

Renewed interest in continuous spinal anesthesia because of the availability of small-bore spinal catheters has led to a number of reports describing its advantages over both single-dose spinal and continuous epidural anesthesia, but few reports describe the catheter's use for postoperative analgesia (1–4). If there are benefits for anesthesia, should there not be benefits for analgesia? Experience with both intrathecal narcotics and PCA led to our combined approach for this patient's postoperative pain management.

A recent study evaluating continuous intrathecal lidocaine infusions for postoperative analgesia found them extremely effective (5); yet other reports suggest that maldistribution and a relatively high dose of local anesthetic may lead to neurotoxicity (6,7). Therefore, we elected to use opioids alone. The high lipid solubility of fentanyl allows for rapid onset of analgesia and limited rostral spread. This results in minimal respiratory depression and a short duration of effective analgesia (3–4 h). Patient-controlled analgesia adds a psychologic advantage to postoperative pain management (8). The interval between the onset of pain and delivery of analgesic medication is minimized, and the measure of patients' control over their own problem undoubtedly plays a significant role in overall comfort and satisfaction.

The most serious potential complications associated with this technique include subarachnoid infection, postdural puncture headache, and respiratory depression. Although the incidence of infection should be no different than for a continuous epidural catheter, the sequelae of meningitis may be far greater. Recent studies suggest, however, that colonization and subsequent central nervous system infection should not be a commonly encountered problem (9,10). Postdural puncture headache remains a controversial issue. Denny et al. (11) recently reported the incidence of postdural puncture headache to be 1.1% among a patient population with a mean age of 63 yr (18-gauge Hustaud needle, 20-gauge catheter). Others have shown a postdural puncture headache rate of 4% and 13% with various sizes of needles and catheters (1,12). Of note, the mean age of patients in these studies was significantly less than 63 yr. Suffice it to say that the smallest catheter available should be used in the youngest patients. Respiratory depression should be limited if vigilant patient assessment is performed hourly and optimal therapy is established. The most common problems with PCA therapy are related to operator errors, not the drug or the pump (13). This patient was sent to the stepdown unit postoperatively only because of the duration of her procedure and her overall medical condition. Ready (14) clearly showed that with extensive nursing education, hourly observation for sedation and ventilatory rate, protocols for immediate treatment of complications, and immediate availability of medical personnel, patients can be cared for on conventional hospital wards without special monitors.

Recently, Glass et al. (15) used a PCA pump to establish the efficacy of epidural versus intravenous administration of fentanyl. They found that once equieffective analgesia was obtained, both fentanyl utilization and plasma concentrations were similar between the two routes of administration. They suggest that there is little advantage to the epidural administration of fentanyl, because its high lipid solubility leads to rapid systemic absorption. The mean hourly cumulative dose of fentanyl in this 12-h study was 52.1 μg (VAS 2–4). During the first 12 postoperative hours, our patient used a total of 60 μg and thereafter approximately 2 μg/h of fentanyl for the next 24 h (VAS 3–5). Perhaps intrathecal administration of fentanyl will prove to be more efficacious than either epidural or intravenous infusions, because substantially lower dosages of fentanyl may be required to achieve adequate analgesia.

Ideal therapy for postoperative analgesia should provide rapid onset of analgesia, easy control, limited tolerance, and few or no side effects. Further investigation of patient-controlled spinal analgesia with fentanyl is necessary to define its role as another modality for postoperative pain management.

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A Rare Case of Perineal Pain: Intestinal Perforation Caused by a Press-Through Package

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Patients with advanced rectal cancer sometimes complain of perineal or pelvic pain, or both (1,2). One patient who had undergone surgery for rectal cancer 10 yr earlier visited our pain clinic complaining of perineal pain. We assumed that the pain was due to a local invasion of recurrent cancer, and caudal blocks were performed. A laparotomy was performed because a vesicointestinal fistula was suspected during the pain management. A press-through package (PTP) was found within a mass of abscess in the pelvic cavity, with one portion of the intestine perforated. After the laparotomy, the patient was discharged and was pain free. A case of fatal fecal peritonitis resulting from colon perforation caused by plastic sheeting has been reported (3). We present a rare case of perineal pain caused by intestinal perforation that had occurred 12 mo earlier after the accidental ingestion of a PTP.

Case Report

A 50-yr-old woman of normal intelligence who had undergone a low anterior resection with end-to-end anastomosis for rectal cancer 10 yr before complained of sudden lower abdominal pain. She had also had an uneventful cholecystectomy for acute cholecystitis 3 mo earlier.

The patient underwent many examinations without detection of abnormal findings, and after treatment with oral analgesics, the abdominal pain decreased gradually, except for persistent perineal pain. Because the pain was continuous and unresponsive to analgesics, we suspected that it was due to local recurrence of the patient's rectal cancer, although there was no evidence to support this.

The patient reported to our pain clinic 11 mo after the appearance of the sudden lower abdominal pain. Because she complained of perineal pain only, a caudal block with 10 mL of 0.25% bupivacaine was performed. She complained of feeling pressure at the caudal region during the injection of anesthetics. Moreover, the pain did not disappear after the block. Caudal blocks were performed five times every other day with no improvement over the first block.

With the sixth caudal block, we aspirated purulent discharge through a block needle. We administered antibiotics locally and orally, suspecting that the infection was caused by our needle. Two days later, her urine was a muddy yellow and smelled of stool. The patient was referred to the surgery department because of a suspected vesicointestinal fistula. After detailed examinations by urologists, gynecologists, and surgeons, a laparotomy was performed because a recurrence of rectal cancer was suspected.

During the procedures for detaching the adhered intestines, a purulent discharge appeared from a space between the urinary bladder and uterus. The abscess occupied a space created by the cystic bladder as the frontal wall, the uterus as the posterior wall, and a lump of adhered small intestines as the upper wall. After the abscess was drained, a PTP containing an intact tablet was found (Figure 1), and a perforated portion of small intestine was confirmed. Anastomosis between the small intestines was performed; however, the vesical fistula did not need a surgical closure. The patient's complaints disappeared postoperatively, and she was discharged 2 wk after the operation.

She could not remember when she took the tablet embedded in the PTP, but she mentioned that she might have taken it along with other drugs in the darkness of a bedroom at night several weeks before the sudden onset of the abdominal pain.

Discussion

Intestinal obstruction resulting from ingested foreign objects is common, but perforation is rare (4). Button battery ingestion in infants and children has been reported, but these objects are usually safe (5). Surgical sponges retained postoperatively do not cause a

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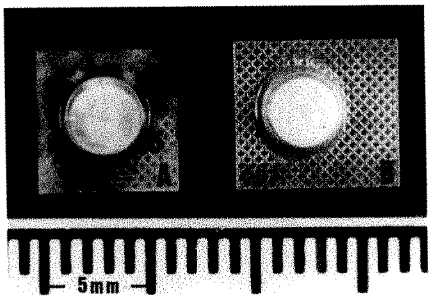

Figure 1. **(A)** A press-through package with an intact tablet found in an intestinal abscess. **(B)** An identical, new tablet embedded in a PTP.

significant problem, except in rare cases of related abscess (6,7). Considering the type of operation previously performed in this patient for rectal cancer, there would be no cause-effect relation between the operation and colon perforation. Severe cases of intestinal perforation resulting from ingested fish bones (8) and a chicken bone (4) have been reported. In the latter case, an ingested chicken bone perforated the colon. Only one fatal case of intestinal perforation after ingestion of plastic sheeting from a PTP has been reported (3). This case, involving a mentally retarded patient, showed severe fecal peritonitis, and a PTP was found by autopsy.

A PTP consists of a dome of vinyl chloride and a thin aluminum lid. Because this container is very easy to separate and carry, many drugs are packaged in this way; however, after a PTP is separated, each corner has sharp edges. If ingested accidentally, it becomes a dangerous foreign body. Moreover, PTPs are unfortunately radiolucent, so their presence cannot be confirmed by radiographic examination. A nondiagnosed radiolucent plastic coin that remained impacted for 11 mo in the esophageal wall of a child was reported (9). In our patient, approximately 12 mo passed before the PTP was discovered.

We believe that the internal pressure in the patient's abscess was high and that the purulent discharge flowed out from the closed space of the abscess during laparotomy. Moreover, a vesical fistula between the abscess occurred 2 days after aspiration of the purulent discharge. When the purulent discharge was aspirated from the caudal space, we thought that the infection was caused by the caudal blocks. Because the caudal space was anatomically close to the intraabdominal abscess, we believed that the infection in the caudal space was due to spread from the abdominal abscess through coarse tissues within the sacral foramina. The complaint by the patient of pressure during caudal block may also support this possibility.

In summary, we present a rare case of perineal pain caused by ingestion of a PTP. Ingestions of PTPs are almost always due to patient carelessness, although a case of mental retardation has been reported (3). In our pain clinic, we sometimes prescribe drugs for episodes of pain. It is therefore possible that the accidental ingestion of a PTP may occur because of impatience experienced by the patient during severe pain. In our medical practice, we need to ensure that there is sufficient workup before the treatment of chronic pain, and if repeated blocks are unsuccessful, another etiology, such as ingestion of a radiolucent foreign body, should be suspected as a possible cause of chronic perineal pain.

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Superior Laryngeal Nerve Block as a Supplement to Total Intravenous Anesthesia for Rigid Laser Bronchoscopy in a Patient With Myasthenic Syndrome

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Myasthenic syndrome, also known as Eaton-Lambert or Lambert-Eaton syndrome, is typically characterized by proximal limb muscle weakness. Patients with myasthenic syndrome demonstrate an increased sensitivity to all muscle relaxants, resulting in unpredictably prolonged weakness that may persist for many days. The response to anticholinesterase drugs in these patients is poor (1).

This report describes the use of superior laryngeal nerve block as a supplement to total intravenous anesthesia for rigid laser bronchoscopy to avoid muscle relaxants in a patient with myasthenic syndrome. This anesthetic technique has not been previously reported in the patient for whom muscle relaxants are relatively contraindicated.

Case Report

A 69-yr-old woman, weighing 73 kg, with myasthenic syndrome was scheduled for rigid laryngoscopy and bronchoscopy for subglottic stenosis. The diagnosis of myasthenic syndrome was made 7 mo earlier when she developed respiratory failure, requiring mechanical ventilation for 59 days. A tracheotomy was performed at that time. A thorough examination revealed no evidence of malignancy, although she had required mechanical ventilation for 5 days after a routine cholecystectomy several years earlier. Her trachea was eventually extubated, and she was discharged.

The patient presented 5 mo after discharge with a 1-wk history of dyspnea and a tingling sensation in her arms, legs, and trunk. Physical examination revealed no significant change in muscle strength from her previous clinic visits. Admission medications included prednisone (60 mg/day) and a thiazide diuretic for hypertension. Arterial blood gases on admission were pHa 7.45, $Paco_2$ 45 mm Hg, Pao_2 79 mm Hg, with an inspired O_2 concentration of 0.21. Initial forced vital capacity was 1.15 L. Airway films revealed tracheal stenosis at the level of the previous tracheotomy site. She was evaluated by the otolaryngology service and scheduled for CO_2 laser ablation of the stenotic lesion.

The patient was orally premedicated with famotidine (20 mg) and metoclopramide (10 mg). After breathing oxygen, anesthesia was induced with propofol (2 mg/kg IV), followed by assisted and then controlled ventilation through a mask with 1.25% expired isoflurane for 10 min. Bilateral superior laryngeal nerve blocks were performed with 3 mL of 2% lidocaine. Direct laryngoscopy was performed without difficulty. A 6.0-mm Rusch red rubber endotracheal tube wrapped with foil tape was used for intubation. The cuff was inflated with sterile normal saline solution. Anesthesia was initially maintained with isoflurane.

Direct laryngoscopy by the otolaryngologist revealed no significant laryngeal abnormalities. The endotracheal tube was then removed and a rigid bronchoscope introduced. Satisfactory ventilation was achieved with a Sanders jet ventilator through the rigid bronchoscope with an initial inspired O_2 concentration of 1.0. Isoflurane was discontinued, and a propofol infusion was started at 150 $\mu g \cdot kg^{-1} \cdot min^{-1}$.

A small area of stenosis was noted 3 cm inferior to the glottis. This area was ablated with the CO_2 laser. Just before and during each use of the laser, the inspired O_2 concentration was decreased to 0.21 by dilution with air through an air-oxygen blender.

The rigid bronchoscope was removed. Ventilation was then controlled by a mask for 10 min as satisfactory spontaneous respiration resumed. Acceptable hemodynamic control was achieved with this anesthetic technique. The patient's systolic arterial pres-

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sure was maintained within 30% of the preoperative baseline blood pressure, and her heart rate ranged from 60 to 80 beats/min. She was taken to the postanesthesia care unit in good condition and was discharged 2 days later with no stridor or complaints of dyspnea. No muscle relaxants were administered, and a stationary field was maintained throughout the procedure.

Discussion

Myasthenic syndrome is a disorder of neuromuscular transmission involving the presynaptic membrane. The etiology is thought to involve the development of IgG antibodies to voltage-gated calcium channels on the presynaptic membrane, inhibiting calcium flux, and thereby blocking acetylcholine release (2). The antibodies cross-react with the calcium channels on the surface of neural crest tumors, including small-cell lung carcinoma. Associated malignant tumors are seen in 72% of men and 32% of women patients with myasthenic syndrome (3). There may be improvement when tumors are removed.

The clinical features of myasthenic syndrome include proximal limb muscle weakness, myalgias, urinary retention, constipation, dry mouth, and impotence. In contrast to myasthenia gravis, the weakness typically affects the lower extremities, fluctuates in severity, and improves with exercise (1,3). In addition, ocular, bulbar, and respiratory muscle involvement are rare in myasthenic syndrome.

The diagnosis is confirmed by electromyography (EMG), which reveals a decremental response at low rates of stimulation and a marked incremental response at high rates of stimulation (3). Tetanic stimulation results in a progressive increase in muscle strength. Posttetanic potentiation is marked (1). The motor unit potential is small and of short duration. The electromyogram in myasthenia gravis reveals a decremental response to stimulation with a normal motor unit potential.

Anticholinesterases such as pyridostigmine have been used to improve neuromuscular transmission but are relatively ineffective in patients with myasthenic syndrome. Guanidine increases the duration of the action potential, but its use is limited by its marked bone marrow, renal, and hepatic toxicity. 4-Aminopyridine and its less central nervous system-toxic derivative 3,4-aminopyridine block voltage-dependent potassium conduction, prolonging depolarization and thereby enhancing voltage-dependent calcium influx, with resultant increases in quantal release of acetylcholine. Although it has limited availability, 3,4-aminopyridine in a double-blind, placebo-controlled study resulted in improvement in all patients with myasthenic syndrome with little toxicity (3,4). Recently, 3,4-aminopyridine was administered postoperatively to a patient with myasthenic syndrome who had been taking it preoperatively and who had an ineffective reversal of vecuronium with neostigmine. Prompt return of neuromuscular function ensued (4).

Chronic immunosuppression has been described as the most effective therapy for long-term symptom control. Although complete remission is rare, some clinical improvement has been observed with corticosteroids, azathioprine, and plasmapheresis (3,4).

Patients with myasthenic syndrome present a challenge to the anesthesiologist because of their extreme sensitivity to muscle relaxants and the potential for prolonged weakness for many days postoperatively.

Inhaled anesthetics have been recommended when muscle relaxation is required. If this is not satisfactory, short-acting muscle relaxants in small incremental doses can be used when anticipating prolonged postoperative residual neuromuscular blockade. A neuromuscular blockade monitor should be used to assist in the incremental dosing of muscle relaxant. Nondepolarizing agents should be reversed as usual at the conclusion of the procedure; however, patients with myasthenic syndrome respond poorly to anticholinesterases (1).

Upper airway lesions are often treated with laser bronchoscopy. A stationary field is mandatory to avoid injury to the surrounding tissues. General anesthesia is the preferred method for laser bronchoscopy. However, inhaled anesthetics have the significant disadvantage of producing operating room pollution when scavenging capability is limited, such as during rigid bronchoscopy. Nitrous oxide should be avoided because of its propensity to support combustion (5). Total intravenous anesthesia avoids these problems. In most patients, muscle relaxants are used concomitantly, because propofol alone, even in high doses, provides inadequate intubating conditions for most patients (6).

Superior laryngeal nerve blocks provide anesthesia to the epiglottis, aryepiglottic folds, and laryngeal structures to the false cords. Contraindications to superior laryngeal nerve block include coagulopathy, full stomach, and local pathology. Superior laryngeal nerve block was recently shown to attenuate the hemodynamic and catecholamine release associated with laryngoscopy in a group of patients undergoing coronary artery bypass grafting (7).

Should inadequate conditions for bronchoscopy have resulted, the alternative plan was to administer small, incremental doses of an intermediate-duration nondepolarizing muscle relaxant, maintaining at least 10% twitch height, if possible. At the conclusion of the procedure, an anticholinesterase agent would be administered to reverse the muscle relaxant. Muscle relaxants have been successfully reversed without difficulty in patients with myasthenia gravis with maintenance of 10% twitch height by giving approximately 10% of the usual dose of pancuronium (8). Despite the marked dissimilarities of the two diseases, it was hoped that muscle relaxants would be as reversible in this patient with myasthenic syndrome as in normal patients with a twitch height of 10% before reversal (9). However, the anesthetic literature refers to the ineffectiveness of anticholinesterases and the unpredictability of prolonged duration of muscle relaxants in myasthenic syndrome (1,2,4). 3,4-Aminopyridine was not available to us should reversal with anticholinesterase have been inadequate.

In this particular case, it was feared that the administration of muscle relaxants could produce profound weakness, necessitating prolonged mechanical ventilatory support that would result in further exacerbation of her tracheal stenosis. The patient's extreme sensitivity to muscle relaxants had already been demonstrated several years earlier, when she required mechanical ventilation for 5 days following a cholecystectomy after having been given pancuronium.

Thus, muscle relaxants were relatively contraindicated in this patient; however, a stationary surgical field was mandatory to avoid laser injury to surrounding tissues. An inhaled anesthetic was not feasible because the patient was jet ventilated through the rigid bronchoscope. Prompt extubation after laser bronchoscopy decreases the likelihood of recurrent tracheal stenosis.

In summary, the use of superior laryngeal nerve block and total intravenous anesthesia provided a number of advantages during laser bronchoscopy: (a) facilitation of intubation and bronchoscopy in a patient who had not received neuromuscular relaxants; (b) neuromuscular relaxation of the upper airway, and (c) decreased anesthetic requirements. This technique may prove useful for patients with other disease entities in which muscle relaxants are relatively contraindicated.

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Letters to the Editor

Difficult Endotracheal Intubation

To the Editor:

I read with great interest the letter to the editor by Benson (1). The use of a gum-elastic bougie for difficult intubation seems to have been practiced in the United Kingdom since its introduction in 1949 (2) and as a first choice when the cords cannot easily be seen at laryngoscopy at Cardiff (3), but this is not so in the United States. We have developed an alternative device for difficult intubation when only the epiglottis is visible at laryngoscopy: a J-, hockey-stick-, or golf-club-shaped endotracheal tube (ETT) which is shaped by immersion in iced water (4).

In practice, when the tip of the epiglottis comes into view on laryngoscopy, the epiglottis is lifted with the tip of the ETT which is then guided beneath the inferior surface until the glottis is passed. During this maneuver, an assistant maintains gentle backward pressure on the cricoid cartilage to prevent esophageal intubation. The assistant also presses on the area of the neck that provides the best view of the epiglottis. As the tip of the ETT gradually softens at room and body temperatures, the tube is advanced while the angle becomes less acute and more easily enters the trachea. Simultaneously, the assistant confirms passage through the glottis by tactile sensation. Insufflation of oxygen can be carried out as intubation proceeds. In an awake patient, elicitation of persistent cough indicates successful intubation. In an anesthetized patient, when the tip of the ETT is located at the glottis, ventilation can be accomplished by an assistant as intubation progresses. A stylet cannot be used with this method as it might not easily be removed owing to the angle of the ETT tip. Armored ETTs made of silicon rubber cannot be used for this technique, but a Mallinckrodt reinforced polyvinylchloride ETT (Glens Falls, N.Y.) can be used. For more than 25 yr, we have not been obliged to use fiberoptic bronchoscopy, a light wand, a stylet, or a gum-elastic bougie for endotracheal intubation when the epiglottis is visible at laryngoscopy.

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Should the Anesthesiologist Estimate the Patient's Weight?

To the Editor:

Anesthesiologists are frequently called upon to anesthetize a patient without an accurate measurement of the patient's weight. Because the appropriate dose for many drugs administered during anesthesia is weight dependent, we frequently either ask the patient to estimate his or her own weight, or we estimate it ourselves. No information is available to tell us which estimate is most accurate, or indeed if either estimate is accurate.

After obtaining institutional approval and patient consent, we studied the weights of patients presenting to our ambulatory surgery clinic. Four resident anesthesiologists and 174 patients participated in the study. The anesthesiologist first estimated the patient's weight, then asked the patient for an estimation of weight, and then finally measured the patient's weight.

We found that the residents' estimation deviated from the patient's actual weight by an average of 8% ± 10% (standard deviation), and that the patients' estimation deviated from their own weight by an average of 4% ± 4% (standard deviation). While it is probable that neither average deviation is clinically significant, the spread of the estimates may be clinically significant. The patient's estimation of weight (range 16.7% under to 11.5% over) was more likely to be close to the actual weight than the anesthesiologist's estimation (range 52.6% under to 18.6% over).

We have concluded that, for any given patient, the anesthesiologist's estimation and the patient's estimation of patient weight may be significantly incorrect. However, the patient estimation is likely to be closer to the actual weight.

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Ralph Waters' Ghost and the AUA

To the Editor:

We read with great interest Dr. Papper's description of the formation of the Association of University Anesthesiologists (AUA) (1). It is rare to have one of the major protagonists comment on events 30 yr later. Yet, this type of paper is important for it demonstrates the necessity of having documents enhanced by the memory of those involved. Often in historical assays this combination is not possible.

Without the foundation in academic anesthesiology provided by Ralph Waters and his disciples, however, it is questionable whether the AUA would have had sufficient strength to form. Of the four original founding members, only Beecher was trained outside of Waters' influence. Of the founding 37 members, 22 (59.9%) were trained within the Waters' sphere (L. E. Morris. The Waters' Tree. Unpublished). Beecher and his group totaled seven members (18.9%), and Lundy's legacy was three members (8.1%). The remaining five (15.5%) of the founders were trained at various locations in the United States and Canada (2).

The requirement that candidates of the American Board of Anesthesiology (ABA) be members of the American Medical Association (AMA) and the American Society of Anesthesiologists (ASA) was "left over" from the original quest for specialty status for anesthesiologists. The New York Society of Anesthetists, which in 1936 became the ASA, created a new class of membership called "Fellows" for the expressed purpose of delineating specialists. Rigid adherence to AMA guidelines allowed the fellowship requirements to ostensibly become those of the ABA when the Board was formed 1938. Owing to the small number of physicians specializing in anesthesia in the late 1930s, it was necessary to enlist the aid of more powerful, established organizations such as the AMA to ensure that diplomates of the Board were recognized as practicing a medical specialty (3). Consequently, to win AMA approval, one of the requirements was AMA membership.

Finally, it is interesting to note that Waters and Rovenstine shared differing views with respect to the political establishment of organized anesthesia. As Waters wrote to Rovenstine in 1935, "You do not realize it but every single thing you or I do . . . tends to antagonize the old wheel horses of the anesthesia organizations" (4). Waters felt that the establishment of teaching within university centers was one way in which anesthesiology would continue to develop. That the AUA exists is also a credit, however indirect, to the vision of Ralph Waters.

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3. Letters from Paul Wood to F. H. McMechan, 1936–1938. In: The collected papers of Paul Wood, M.D., Park Ridge, Ill.: Wood Library-Museum of Anesthesiology.
4. Letter from Ralph Waters, M.D. to Emery Rovenstine, M.D., June 24, 1935. In: The collected papers of Ralph Waters, M.D. Madison, Wis.: Steinbock Library Collection of the University of Wisconsin.

In Response:

I am pleased that these two able anesthesiologists, Drs. Bacon and Lema, thought that my article describing the beginnings of the Association of University Anesthesiologists was of great interest and also, in their opinion, important.

All of us who are descended intellectually and professionally from Ralph Waters are very proud of our heritage and enjoy the recognition that it confers on us. Of the founding four members, I had the additional unique privilege of being a resident of Dr. E. A. Rovenstine who was Dr. Water's first and probably most distinguished disciple. The issue, however, of our anesthetic origins, while important, was not viewed by the Founding Four as crucial to AUA. We felt, and I still think correctly so, that University Anesthesiology should comprise all the academically talented people regardless of their origins—and in my own opinion—irrespective of those origins.

The discussion that Drs. Bacon and Lema provide about the relationships of the American Board of Anesthesiology and the American Medical Association do not seem to me to explain the problems we encountered in the earliest days of the AUA. They are certainly of interest and I'm sure that those concerned with the history of organized medicine and specialities will find that information of value to them.

Finally, I think it is necessary to state that the hard work of a small group of individuals, as we were then, depended heavily upon our productivity rather than our professional ancestry. If I had to guess, I would think that Dr. Waters would have been very supportive and proud of the AUA as the manifestation of academic youth and vigor in the field to which he contributed so much.

Although it appears only tangentially in my original article, I can assure Drs. Bacon and Lema that Emery Rovenstine was very supportive of what we were doing and was very pleased that we wanted him to be one of the first elected members. He told me many times that new paths must be found to address new problems. He understood then, as I believe I understand now, that without change there is no progress. However, change, per se, does not identify automatically with progress. That is why continuous and evolving brilliant leadership is necessary to make our specialty the living and dynamic organism that it can be.

No ghost is required with those attitudes. The freedom of descendants to be original in no way vitiates the affection and respect all of us have for Ralph Waters—the man who made most of us possible and is permanently enshrined in the pantheon of the anesthetic gods. The Ralph M. Waters Award that I was privileged to receive is among my most cherished possessions.

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Suicide Attempt After Anesthesia

To the Editor:

A 58-yr-old man was admitted to a municipal hospital for an inguinal herniorraphy. He was otherwise healthy and was taking no medications. He had a negative medical and psychiatric history but was described as being excessively talkative, and the resident who took the history believed that the patient might be having paranoid delusions. Although a psychiatric consultation was requested, it was not carried out before the surgical procedure. The patient received general anesthesia (isoflurane, nitrous oxide, midazolam, fentanyl, thiopental, and atracurium) and had the hernia repaired. He had an uneventful recovery in the postanesthesia care unit, and there were no reports of unusual behavior. Several hours later, after the patient had been discharged to the ward, he was found on his bed with a deep bleeding wound across the neck. He was taken to the operating room, the neck was explored, and the hemorrhage was brought under control. He later admitted that he had tried to kill himself with a razor blade and was diagnosed as suffering from schizophrenia.

Many factors surrounding anesthesia and surgery may trigger emergence delirium and postoperative psychosis. These include drugs, fever, pain, hypoxia, metabolic derangements, and psychological factors (1). This patient was already suffering from an undiagnosed psychiatric disorder that made the initial differential diagnosis somewhat difficult.

The incidence of schizophrenia is much higher in the lower socioeconomic groups (2). Given the fact that municipal hospitals tend to serve this patient population, a high index of suspicion should be maintained in this setting. An elective preoperative psychiatric evaluation may be warranted in a patient suspected of suffering from a mental illness. This will not only help with the differential diagnosis of postoperative psychosis, but may also and most importantly, prevent the patient from harming himself or others.

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How Does Epidural Anesthesia and Analgesia Influence Perioperative Coagulability?

To the Editor:

We read with great interest the editorial by Steele and colleagues (1) accompanying the paper by Tuman et al. (2). We would like to commend Steele et al. for their review of the current literature regarding the influence of epidural anesthesia and analgesia (EAA) on perioperative coagulability. Tuman et al. have put forth an outstanding effort that helps better differentiate why those of us performing general anesthetics with epidural catheters placed for postoperative pain control believe that this is superior to the more traditional approach of general anesthetics with on-demand postoperative analgesics (intermittent intramuscular, intravenous, or oral pain medications).

Anesthesiologists have discovered that appropriate management of perioperative hemodynamic abnormalities can influence outcome in "high-risk" patients, although stable perioperative hemodynamics do not necessarily ensure uneventful cardiovascular outcome. Tuman has put forth an interesting proposal of "perioperative hypercoagulability" as another issue that must be dealt with in "high-risk" patients. How blockade of the "perioperative stress response" may influence this propensity for hypercoagulability in the postoperative period is still not well understood.

We would like to qualify and expound upon one idea put forth in the editorial by Steele et al. stating: "Fibrinogen, a glycoprotein essential to hemostasis and blood viscosity, is frequently increased in patients with vascular disease. Perhaps EAA reduces fibrinogen." It is important to remember that the half-life of fibrinogen in humans is 3–4 days and in Tuman's study the average utilization of epidural catheters was 2.4 ± 0.98 days. Speculation that this intervention, administered for such a period of time, would influence fibrinogen levels significantly in the postoperative period must take the long half-life into account. It might be that augmented fibrinogen production is reduced by EAA, although this will be difficult to prove in clinical studies owing to the large variability involved in performing functional fibrinogen assays.

Fibrinogen plays an essential role in hemostasis and the maintenance of blood viscosity. It mediates the formation of platelet aggregates and, in the coagulation cascade, is transformed by thrombin into fibrin monomers that polymerize to form the basis of a hemostatic plug. Ten to twenty-five percent of the total body fibrinogen is extravascular. Of the circulating fibrinogen in blood, about 3% is located in the platelet alpha granules, although it is unclear if this is the result of fibrinogen biosynthesis by megakaryocytes or due to platelet uptake from the plasma. Plasma levels of fibrinogen and a subset of other hepatic proteins increase during the "acute-phase response" to injury and infection (3). For fibrinogen, the protein level reflects a coordinated increase in the hepatic production of the mRNAs that direct the synthesis of the three pairs of nonidentical polypeptide chains that compose fibrinogen. The increase is predominantly in response to interleukin-6 (IL-6) produced by monocytes/macrophages. Interleukin-6, a key mediator in the inflammatory response, preferentially stimulates the synthesis of fibrinogen in human hepatoma cells. Whether the influence of EAA on the stress response may have some effect on the inflammatory response is unknown. The effects of stress on the inflammatory response are likely complex. Perhaps EAA decreases hypercoagulability by direct or indirect modulation of the inflammatory response (decreased production of IL-6) and subsequent inhibition of the "acute-phase response." Little is known about the influence of general anesthesia on the cytokine network, although ongoing studies at our institution have initially shown that the induction of general anesthesia has no significant immediate influence on levels of IL-6. The effect of postoperative epidural administration of local anesthetics and/or narcotics on IL-6 levels is unknown.

We support the approach taken by Tuman and colleagues of utilizing the thrombelastograph as a tool to measure fibrinogen-platelet interactions in the postoperative period, and believe that the most likely explanation for their results is an inhibition of the release of "stress-related" hormones, and subsequent inhibition of platelet adhesion-aggregation that is normally augmented by these stress hormones. Although not examined in the study of Tuman et al., another explanation may be inhibition of the "acute phase response" in the postoperative period, which if prolonged may predispose patients to development of a hypercoagulable state secondary to augmented fibrinogen synthesis. Further studies closely examining the influence of EAA on the inflammatory response may help further delineate the beneficial influence of postoperative epidural analgesia on morbidity/mortality in the surgical population.

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In Response:

We thank Whitten et al. for their affirmative comments about our manuscript and compliment them for the additional insight they provide into potential mechanisms by which EAA influences coagulation. We agree with Whitten et al. that if EAA is indeed associated with lesser postoperative levels of circulating fibrinogen in patients with vascular disease, this may possibly be a result of inhibition of the "acute-phase response" with attenuation of augmented fibrinogen production, but is unlikely to be a result of changes in basal fibrinogen production. Whitten et al. correctly note that the observation of decreases in coagulability as early as 24 h after surgery in patients receiving EAA is inconsistent with the pharmacokinetics of basal fibrinogen production and metabolism. The most likely explanation for the altered fibrinogen-platelet effects measured on the first postoperative day is inhibition of the release of stress-related hormones such as catecholamines with subsequent reduction in the otherwise increased platelet activity produced by such mediators, as Whitten et al. contend. We further postulate that our findings could be related to decreases in plasminogen activator inhibitor with subsequent increases in fibrin(ogen) breakdown, but additional studies will be necessary to elucidate the exact mechanisms by which EAA influences coagulation.

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Epidural Anesthesia and Analgesia in Vascular Surgery

To the Editor:

We read with interest the recent article by Tuman et al. and the accompanying editorial (1,2). There is convincing evidence that epidural anesthesia and analgesia (EAA) blunts the stress response to surgery (3); but, does this have a positive effect on outcome? Tuman et al. suggest that EAA modifies the coagulation system with salutary effects on adverse thrombotic events. In vascular surgery these adverse thrombotic events can involve either (a) the arterial graft, (b) the coronary arteries, or (c) the venous system. The resulting adverse outcomes are, respectively, (a) graft failure, (b) perioperative myocardial infarction (PMI), and (c) pulmonary embolism secondary to venous thrombosis.

Interpretation of the outcome portion of the Tuman study is difficult. The study population consisted of a heterogenous set of vascular procedures. Apparently, roughly half of the procedures involved infrainguinal reconstruction and the remainder were aortofemoral bypass procedures. It is plausible that EAA-induced changes in coagulation could have a salutary effect on graft failure in infrainguinal procedures. On the other hand, graft failure in aortofemoral bypass procedures is almost entirely due to technical difficulties where anesthetic technique is unlikely to have an impact. Therefore, it would be very helpful to know if the graft failures involved infrainguinal procedures. Tuman et al. note that all the patients who had graft failure had intraoperative arteriograms at the completion of the initial operation. Are completion arteriograms standard at the study institution or did the operating surgeons obtain them in these cases because technical difficulties were already suspected?

If indeed, graft failures in the control group all involved infrainguinal procedures, the relevant rate is 8/20 (40%) as half of the 40 control patients underwent infrainguinal procedures. This is much higher than the 5%–10% rate of early graft failure found in comparable series of infrainguinal procedures (4–6). Some retrospective data would be helpful here. What was the rate of early graft failure in the study institution before the initiation of the protocol? If the earlier rate of graft failure was more in line with that reported in other series (<10%), then we are left with the suspicion that, in this relatively small study, the luck of the draw placed a number of difficult, complication-prone procedures in the control group. Other outcome measures

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The authors' opinions should not be construed as representing official views of the Departments of the Army or Defense.

were seriously confounded with the higher incidence of complications in the control group. Intensive care unit (ICU) stay was shorter in the EAA group; however, this appears to be almost entirely attributable to the need for reoperation for early graft failure among the control patients. A larger study may have found shorter ICU stays in EAA-treated patients, even after excluding patients who suffered complications.

It should be noted that there are many relevant variables that can affect the incidence of early graft failure after infrainguinal vascular procedures. Infrainguinal procedures encompass a number of different revascularization techniques: i.e., thromboendarterectomy, patch angioplasty, and bypass. For the bypass procedures, the type of conduit is an important variable: e.g., vein (reversed or in situ), polytetrafluoroethylene (PTFE, Gortex), or dacron. Finally, the site of distal anastomosis is important, e.g., suprapopliteal, infrapopliteal, or more distal. Assuring that this myriad of variables is comparable between control and treatment groups will be a daunting task for any future trial attempting to assess the effect of EAA on early graft failure.

One outcome measure in the Tuman study may not have been confounded with the higher incidence of graft failure in the control group, PMI. There were three PMI in the control group and none in the EAA group. Apparently these three cases did not involve any of the vascular complications. The *P* value for this difference was 0.07, which in a small study is at least suggestive that EAA could have a salutary effect on the incidence of PMI. Vascular surgery patients are at high risk for concomitant coronary artery disease, and PMI is a serious problem. Pathophysiologically, it seems plausible that the salutary effects on coagulation proposed by Tuman et al. could decrease the incidence of PMI in vascular patients. A recent, large prospective series comparing general and epidural anesthesia for infrainguinal arterial reconstruction found no difference in the incidence of PMI (7). However, in this study EAA was not continued into the postoperative period. As PMI often occurs in the first several postoperative days, rather than specifically during the operation, it appears that the stress response must be blunted well into the postoperative period to have a significant salutary effect on PMI. It is also not clear if postoperative epidural opioids would be sufficient or, as in this study, a combination of opioids and local anesthetics is required.

As mentioned in the editorial, outcome data must be forthcoming to justify the time and expense involved with EAA. We believe that Dr. Tuman and colleagues have provided a useful working hypothesis; but, unfortunately, this small study does not represent definitive outcome data.

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In Response:

Baumgarten et al. provide insight into our work from a surgical viewpoint, and we are pleased to comment on their analysis of our study (1). Baumgarten et al. astutely note that most vascular graft failures after aortobifemoral bypass procedures are likely associated with technical difficulties. This does not, however, mean that hypercoagulability could not contribute to graft failure in these cases. Specifically, when technical difficulty is encountered during aortoiliac reconstruction, this is typically related to poor femoral anatomy in patients with severe aortoiliac atherosclerotic occlusive disease. Reduction of iliofemoral arterial lumen with less than optimal blood flow distal to the reconstruction can lead to inadequate limb perfusion, which probably can be compounded by a hypercoagulable state. Even though the frequency of this scenario is far less than seen with infrainguinal procedures, a salutory effect of epidural anesthesia and postoperative analgesia on coagulation as well as improvements in lower extremity blood flow secondary to central neuraxial sympatholysis could plausibly reduce graft failure in both types of procedures. This is consistent with our findings that there were two vascular graft failures in 20 suprainguinal procedures randomized to the GEN group, whereas none of the 15 suprainguinal procedures randomized to the GEN-EPI group were associated with graft failure. The distribution of complications according to type of revascularization and anesthesia group is shown in Table 1 and confirms that most of the graft failures involved infrainguinal procedures.

Table 1. The Distribution of Complications According to Type of Revascularization and Anesthesia Group

	All cases		Infrainguinal revascularization		Aortoiliac reconstruction	
	GEN	EPI	GEN	EPI	GEN	EPI
No. of cases	40	40	20	25	20	15
No. vascular graft failure	8	1	6	1	2	0
No. deep venous thrombosis	1	0	1	0	0	0
No. myocardial infarctions	3	0	1	0	2	0
No. thrombotic complications[a]	11	1	7	1	4	0

GEN, general anesthesia; EPI, epidural anesthesia.
[a] Number of patients with thrombosis of vascular graft, coronary artery, or deep leg vein, not number of individual occurrences; one patient had both myocardial infarction and vascular graft failure.

Even though the subpopulation undergoing infrainguinal revascularization was smaller than the overall study population, statistical significance was still achieved when comparing the incidence of vascular graft failure in the GEN-EPI group (1/25) with that in the GEN group (6/20; $P = 0.017$). Completion arteriograms are standardly performed at our institution for all patients undergoing infrainguinal revascularization, and as noted in our paper, none of the patients with vascular graft failures had evidence of technical problems such as intimal flap or anastomotic problems and all had evidence of adequate outflow on completion of operation. The two patients who experienced lower extremity ischemia after aortoiliac reconstruction both had postoperative arteriograms that demonstrated no technical problems related to the graft or anastomotic sites, but did reveal residual atherosclerotic involvement infrainguinally that was not thought to be significant during the preoperative surgical evaluation. Both of the latter patients were markedly hypercoagulable postoperatively, and we believe that this hypercoagulability contributed significantly to their adverse vascular outcome. We would, however, agree with the implication of Baumgarten et al. that in the absence of abnormalities of vessel architecture (such as endothelial damage or luminal compromise with subsequent aberrations in blood flow patterns and velocity) hypercoagulability is probably much less important to surgical outcome than when such abnormalities are present. Indeed, this is likely to be the very reason that we observed such profound effects on graft failure rate in the infrainguinal group. This subset of patients represents a population at variable but consistently high risk of vascular complications. Simple comparison of overall vascular complication rates is dangerous without careful analysis of population demographics, precise quantitation of vascular anatomy, and evaluation of other subtle but important factors such as perioperative coagulation management (aspirin, low dose heparin or dextran). The overall incidence of vascular complications after infrainguinal revascularization in our study was 15.5% (7/45), and is a reflection of the severity of vascular disease in the study patients. This is consistent with other recently reported data (2) that confirm our findings that epidural anesthesia with postoperative analgesia has a beneficial effect on vascular complications after lower extremity revascularization. The Johns Hopkins experience revealed that regrafting or thrombectomy was more common in 51 patients randomized to general anesthesia than in 49 patients randomized to epidural anesthesia/analgesia (22% vs. 4%, $P < 0.01$) (2), and these results are remarkably similar to those at our institution. The overall rate of graft failure in our study did not differ markedly from that previously observed at our institution and reflects the large number of difficult and complication-prone patients treated for lower extremity revascularization. The similarity of results from two institutions studying the same phenomena strongly suggests that Baumgarten et al. need not be left with the "suspicion that . . . the luck of the draw placed a number of difficult, complication-prone procedures in the control group."

Baumgarten et al. correctly point out that a large number of surgical variables could plausibly affect the incidence of early graft failure after infrainguinal revascularization. Grafting to distal vessels was equally frequent in both randomized anesthesia groups. Most studies suggest that patency rates after lower extremity revascularization are better when saphenous vein is used as the conduit compared to when synthetic materials such as Gortex or dacron are used because of lack of usable vein. In our study, a lower frequency of vein graft use (3/25) in the EPI group compared to the GEN group (7/20) actually represents a reverse bias against the occurrence of better graft patency in the EPI group. During the planning of our study we recognized that the use of synthetic versus saphenous vein graft was a potentially important factor influencing surgical outcome. However, the decision to use Gortex rather than the preferable vein graft can often be made only after intraoperative evaluation of potential native conduits, so that preoperative randomization of anesthesia type matched to a single type of conduit would be impractical and require another study design such as placement of epidural catheters in *all* patients with subsequent intraoperative randomization to an epidural treatment group. Indeed, post hoc evaluation of the 35 infrainguinal procedures that required use of Gortex only confirms the overall findings of our study. In this subset, the incidence of acute vascular graft failure was also very much less in the EPI compared to the GEN group (4.5% vs. 30.8%, $P = 0.033$). For the reasons discussed above, we are confident that more complicated and elaborate study designs that attempt to more closely control for potentially confounding anatomic variables will validate our findings.

We agree with Baumgarten et al. that prolongation of ICU stay has a multifactorial etiology, but refute the contention that prolonged ICU stay "appears to be almost entirely attributable to the need for reoperation for early graft failure." The average duration of ICU stay among the 9 patients in our study with graft complications (2.77 ± 3.6 days) was not significantly different from the 71 patients without graft complications (2.37 ± 5.2 days, $P = 0.82$). A logistic regression model used to predict prolonged ICU stay (>3 days) based on the postoperative complications listed in Table 4 of our paper indicates that cardiovascular and major infectious as well as overall complication rates were the only significant multivariate predictors of prolonged ICU stay. Graft failure, including necessity for reoperation or amputation, had neither a multivariate nor univariate association with prolongation of ICU stay. Not surprisingly, prolongation of ICU stay had the greatest correlation with total number of serious complications, and this in turn had a strong association with type of anesthesia and analgesia.

Finally, we strongly agree with Baumgarten et al. that our findings suggestive of an apparent beneficial effect of anesthetic management on the occurrence of PMI in the EPI group are very likely attributable to the postoperative use of epidural analgesia. A common denominator of prospective studies that have demonstrated beneficial effects of central neuraxial techniques on this outcome is the use of continuous postoperative epidural analgesia. Failure to consistently continue epidural use into the postoperative period is a common feature of all studies that do not demonstrate such salutory effects. Many of the questions raised by Baumgarten et al. are important, and we agree that further critical investigation will be necessary to refine our understanding of the effects of EAA that we have reported in our study.

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Differential Awakening

To the Editor:

I would like to propose a new phenomenologic term, "differential awakening," for the clinical anesthesiologist. Over the years as a practicing neuroanesthesiologist, I and others have observed that patients with cerebral ischemia or mass lesions frequently show evolving lateralizing neurologic signs on awakening. Immediately on awakening, unilateral return of motor function is frequently delayed but improves, and returns to complete function over about 10–30 min, thus, the term "differential awakening."

This process is clinically significant because it is clearly different from a surgical neurologic deficit that is expected to return slowly. It is also different from immediate surgical complications that might require reopening of the cranium or a computed axial tomographic scan for further diagnosis. Three theories could explain the phenomenon of differential awakening. First, anesthetics enter the brain and are trapped in areas that are injured by ischemia or trauma, and at the end of anesthesia, these anesthetics escape more slowly from the injured areas. Second, perhaps the areas of cerebral injury are more sensitive to low concentrations of the anesthetic, resulting in a slower unilateral emergence. Last, in patients who suffer destructive neurologic damage with full recovery, it is believed that secondary pathways compensate and accomplish the function of the destroyed neurons; perhaps these secondary pathways are only functional in a completely awake state.

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Complete Tolerance to Opioids

To the Editor:

Complete tolerance is a well-known, but rarely seen, complication of prolonged opioid administration. Aggressive pain management in cancer patients, who are living longer, is now presenting us with this clinical problem. Cross-tolerance to other drugs makes analgesia even more difficult.

Recently, we treated a 49-yr-old man with intractable pain from a pelvic chondrosarcoma who demonstrated this problem. This patient had received maximal chemotherapy and, for more than a year, had used morphine at home through an intravenous pump. In the hospital, we failed to achieve analgesia or sedation with morphine infused at 1200 mg/h or with hydromorphone at 800 mg/h. A midazolam infusion at 10 mg/h produced little effect. Finally, an intravenous infusion of ketamine, titrated to $2.7\ \mathrm{mg \cdot kg^{-1} \cdot h^{-1}}$, produced satisfactory pain relief while the patient remained awake. Unfortunately, we could not further refine this therapy because the patient died 30 h after starting ketamine.

Current research on opioid receptors reveals three primary types—mu, kappa, and delta—and several subtypes of these. Ketamine acts at multiple thalamic and spinal cord sites, including opioid receptors (1). Ketamine also inhibits the dorsal horn nociceptive receptor stimulated by *N*-methyl-D-aspartic acid (NMDA) (2,3). That ketamine produced conscious analgesia in our opioid-tolerant patient may indicate it inhibited nociceptive pathways through NMDA receptor antagonism. The larger-than-normal ketamine requirement may indicate partial cross-tolerance with morphine, which occurs in animals (4).

Perhaps ketamine or other NMDA antagonists will prove useful as adjuvant drugs in cancer patients receiving high doses of opioids. We would like to see more research or clinical reports in this area.

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Is the "Kneeling" Prone Position as Dangerous as the Sitting Position for the Development of Venous Air Embolism?

To the Editor:

We are extremely impressed with the excellent report by Albin et al. (1) concerning major venous air embolism (VAE) occurring in three patients who were undergoing spinal surgery in the prone "kneeling" position. It would also have been interesting to know the time period over which these three complications occurred.

We inserted pulmonary artery catheters in some of our patients who were scheduled for lumbar laminectomy with fusion and were positioned in the Andrew's frame. These patients had normal myocardial function, and we observed pulmonary capillary wedge pressures (PCWP) ranging from 5 to 7 mm Hg after induction of anesthesia and before positioning in the frame. As soon as the patients were placed in the kneeling position, PCWP decreased to approximately zero accompanied by a similar decrease in central venous pressure (CVP). We elevated the patients' legs while they were still prone before surgery started, with a resulting increase of PCWP and CVP. During these procedures, crystalloids and colloids were given in an attempt to increase CVP. When returning the patient to the supine position at the end of surgery, a marked increase in PCWP and CVP was also noted and required the intravenous administration of furosemide to avoid the development of pulmonary edema.

Based on these observations and the work of DiStephano et al. (2), we presume that the decrease in PCWP is a result of blood pooling in the legs when they are positioned lower than the heart despite the precaution of wrapping the legs in antiembolism elastic stockings (TED hose) with sequential pneumatic compression. We suspect that the kneeling position markedly increases the pressure gradient between the surgical site and the right side of the heart by producing relative central hypovolemia even before surgery is started. This is then aggravated by surgical blood loss, especially with the delay of retransfusion of blood volume imposed by the cell saver that is routinely used in these cases. The relatively low CVP combined with the length of these procedures (8–12 h of surgical time at our institution) obviously predispose to increase the risk of VAE.

We consider that this subject is of the utmost importance and, in our opinion, these procedures should be carried out with the same level of attention that is applied to anesthesia for surgery in the sitting position. Clearly efforts should be made to reestablish a reasonable level of CVP. We agree with Dr. Albin that any occurrence of VAE should be reported in the medical literature so that we can ascertain the true incidence of this complication under these conditions.

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A Special Surgical Technique Leads to Venous Air Embolism During Neurosurgery of the Spine

To the Editor:

Dr. Albin et al. (1) have pointed out the need of reporting cases of venous air embolism (VAE) to estimate its frequency. We would like to report three cases of VAE during neurosurgery of the spine involving the use of homologous spongious bone graft.

The graft was prepared by breaking down bone into small fragments and collecting these fragments in a funnel. This material was then injected into the intervertebral compartment by applying pulsatile pressure with a piston. This technique was used in three patients and led to VAE every time.

The demographic variables are summarized in Table 1. In each case, after graft injection (funnel and piston), a typical millwheel murmur was heard in the esophageal stethoscope with a concomitant decrease in the end-tidal CO_2. The prophylactic placement of a vent catheter in the discal compartment was ineffective in preventing VAE in case 3.

Venous air embolism has been described during lumbar laminectomy (1). The type of positioning of the patient (2), the vena cava pressure (3), and the gravitational gradient right heart-operative field are important factors. So far, the placement of homologous bone has not been associated with VAE. Although no precordial Doppler was installed, the diagnosis of VAE with the aid of the esophageal stethoscope was suspected in each case.

The causative mechanism in our three cases of VAE is thought to have been a "bicycle-pump" phenomenon during graft placement: the pulsatile movement through the funnel creates a high pressure in the discal compartment,

Table 1. Patient Demographics

	Cases		
	1	2	3
Age (yr)	59	51	33
Sex	M	F	M
ASA physical status	III	II	II
Surgery	Laminectomy and fusion L3-S1	Discectomy L5-S1	Discectomy L5-S1
Position	Prone	Prone	Prone
Millwheel murmur (ES)	++	++	++
ET_{CO_2} decrease (mm Hg)	6	10	7
Associated events	Tachycardia, elevated ST-segment	Wheezing	None
Sequelae	None	None	None

ET_{CO_2}; end-tidal CO_2; ES; esophageal stethoscope.

which produces VAE; air enters the venous system either via a peridural vein or via the venous channel of the bone.

In conclusion, injection of spongious graft using a funnel and piston creates high pressure in the discal compartment and leads to VAE. This technique clearly has the potential to enhance the chances of a VAE.

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Resistance to Curare, Upper Motor Neuron Dysfunction, and Antiepileptic Treatment

To the Editor:

We wish to make some comments on the article by Moorthy et al. concerning the resistance to nondepolarizing muscle relaxants (NDMRs) in patients with cerebral palsy and in patients treated with antiepileptic drugs (1).

From a neurophysiologic point of view, curarization (2) and myasthenia gravis (MG) (3) are both assessed by the same diagnostic technique. We think, therefore, that observations made in myasthenic patients could be useful in understanding whether the resistance to vecuronium reported by the authors should be ascribed to pharmacodynamic or pharmacokinetic factors.

In hemiparetic patients who subsequently acquire MG and in myasthenic patients who subsequently acquire hemiparesis, electromyographic evidence of MG is restricted to muscles contralateral to the side of the motor deficit (4,5). In other words, decentralized muscles of patients with upper motor neuron dysfunction may become resistant to antibodies occurring in MG just as they become resistant to NDMRs.

Nondepolarizing muscle relaxants and anti-acetylcholine-receptor (AChR)-antibodies have different mechanisms of action. Junctional AChRs, however, are the common target upon which the action of both is exerted and effects are quantified.

We think, therefore, that the appearance of a new population of junctional AChRs should be regarded as a possible consequence of upper motor neuron dysfunction and as a possible explanation of the resistance to NDMRs exhibited by decentralized muscles.

There are no reports indicating that signs and symptoms of MG can be relieved by the use of antiepileptic drugs. On the contrary, our clinical impression is that the treatment of MG is more difficult when MG is complicated by epilepsia. In other words, antiepileptic treatment may be followed by resistance to the action of NDMRs, but not to the action of anti-AChR-antibodies.

We retrospectively examined the intensity of neuromuscular blockade produced by the tracheally intubating dose of NDMRs (pancuronium or vecuronium) in 72 neurosurgical patients. Decentralization was present in 34 examinations. Motor deficit was not present in the remaining 38. The mean value of T-1 was 37.5% in the paretic patients and 12.8% in the nonparetic patients ($P < 0.001$, one-way analysis of variance). The mean value of T-4 was 22.6% in the paretic patients and 2.2% in the nonparetic patients ($P < 0.001$, one-way analysis of variance).

Chronic antiepileptic treatment was present in 20 patients. No significant correlation was found between antiepileptic treatment and intensity of the neuromuscular blockade. The mean values of T-1 and T-4 were 24.0% and 11.6% in the treated paretic and nonparetic patients, respectively, and 24.5% and 11.9% in the untreated paretic and nonparetic patients. The difference in T-1 and T-4 values between paretic and nonparetic patients was still significant ($P < 0.001$, one-way analysis of variance) when adequate correction for the antiepileptic treatment was performed.

Even though the number of patients is small in our series, we think that our data and observations made in myasthenic patients support the hypothesis that pharmacodynamic factors should be considered in patients with upper motor neuron dysfunction, whereas pharmacokinetic factors should be considered in patients treated with antiepileptic drugs.

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Scientific Approach to Presenting and Summarizing Data

To the Editor:

Descriptive statistics and inferential statistics are the main tools for scientific communication in biomedical journals. Descriptive statistics include expressions of means, standard deviations (SDs), coefficient of variation (CV), proportions, medians, ranges, and percentiles. Inferential statistics include standard errors (SEs), confidence intervals (CIs), and various tests that yield *P* values for differences in means, proportions, and other descriptive data (1). In this communication I would like to suggest some methods to improve the quality of presenting and summarizing data in our journals.

I examined the articles published in *Anesthesia & Analgesia* in the year 1991 to determine how data are presented and summarized. There were 208 articles related to laboratory and clinical investigations. In 90 (43.27%) of these articles, the data were summarized as mean ± SD and in 91 (43.75%) as mean ± SEM. The data in the rest of the articles were summarized as medians, ranges, percentages, etc. The suggestion that all journals discontinue the use of the ± sign was made in 1986 by Altman and Gardner in a letter to the *The Lancet* (2). But this sign continues to appear in the *Anesthesia & Analgesia* journal regularly. It was also stated in the same letter that SEM should not be used to indicate the variability of a set of observations. As mentioned above, in 43.75% of the articles published in 1991, authors used SEM to indicate the variability. Variability is best indicated by SD or CV (SD/mean %) according to the situation (3,4). The CV is most useful as a descriptive tool in situations in which a change in the conditions under which measurements are made alters the SD in the same proportion as it alters the mean (3). Glantz suggested that SD, not SE, should be used to summarize the data (5). The fact that SE is inappropriate for indicating the variability of a sample must be clearly understood. By itself, SE provides limited information. It is used to estimate the CI, which is very informative (6,7). The CI is a range of values that is likely to cover the true, but unknown, population value. Thus SE is an inferential statistic, not a descriptive statistic (8). Confidence intervals can be computed from SEs for every sample statistic (means and their differences, proportions and their differences, correlation coefficients and regression coefficients, etc.) using the standard formulas (3,6,7).

There are several advantages of presenting the data (in tables and figures) as CIs wherever appropriate. Confidence intervals provide more information than hypothesis testing by the use of *P* values (6). Differences of no real interest can be statistically significant with large samples, whereas clinically important effects may not be significant when the sample size is small. Confidence intervals provide useful information in studies with large as well as small samples (9) and help us to avoid some misinterpretations that result from dichotomous conclusions from the significance tests based on *P* values (10,11). In addition, CIs also have a link to the outcome of hypothesis tests. For example, when the result of difference between two means is significant at the 5% level, the 95% CI for difference in their means will not encompass zero (7). Difference in proportions summarized in 2 × 2 tables are usually tested by Fisher's exact test or χ^2 analysis with Yates' correction. But 95% CI for difference in proportions gives more information than hypothesis testing by either of the above two methods. In addition, meaningful interpretations of results of different studies can be derived when the difference in proportions are given in 95% CIs rather than when the results are interpreted by significant testing based on *P* values (12). Finally, according to Snedecor "the purpose of an experiment is to produce a sample of observations which will furnish estimates of parameters of the population together with measures of uncertainty of these estimates" (13). Confidence intervals satisfy the requirements for a meaningful inference from an experiment because they indicate the degree of imprecision of the sample as an estimate of the population value.

In summary, variability in a sample may be presented as SD without the use of the ± sign, or as CV according to the situation. Confidence intervals, if appropriate to the type of study, should be used for major findings in both the main text of the paper and its abstract (6). In the present day and age of rapidly growing medical literature in a plethora of journals, we generally rely on computer-assisted literature search programs to access different publications. As these services allow us to get only the abstracts, the suggestion that the more informative CIs be presented in the abstracts appears very attractive. This letter is essentially an echo of what statistical experts have been expressing during the past few years. The suggestions if followed will further improve the quality of scientific communication in *Anesthesia & Analgesia* and in other journals of our speciality.

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Esterase Nomenclature: A Confusing Topic

To the Editor:

The classification of cholinesterases is so unclear that even leading anesthesiology textbooks carry errors in their description. Page 473 of *Clinical Anesthesia* edited by Barash, Cullen, and Stoelting states that "pseudocholinesterase degrades acetylcholine released at the neuromuscular junction" (1). Instead, it should read "acetylcholinesterase" or any of the other multiple terms used to designate this enzyme.

This letter is not to point out a typographical mistake but to illustrate that esterase nomenclature is very confusing. True cholinesterase (E.C.3.1.1.7) is also known as choline esterase I or specific, cholinesterase, acetylcholine hydrolase, acetylcholinesterase, or erythrocyte cholinesterase. Whereas pseudocholinesterase (E.C.1.1.8) is also known as choline esterase II or unspecific, butyrylcholinesterase, benzoylcholinesterase, acylcholine acyl-hydrolase, serum cholinesterase, or plasma cholinesterase (2,3).

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A Simple Replacement for the Pulmonary Artery Catheter Balloon Syringe

To the Editor:

During the use of a pulmonary artery catheter, the 3.0-mL balloon inflation syringe may be misplaced. This may necessitate replacement with a regular 3.0-mL syringe and the expense of opening a new kit to obtain the special syringe. Manufacturers recommend that no more than 1.5 mL of air be used to inflate the pulmonary artery catheter balloon. If too much air is injected, it can cause balloon or pulmonary artery rupture. We describe a simple and easily accessible method to prevent excessive air injection.

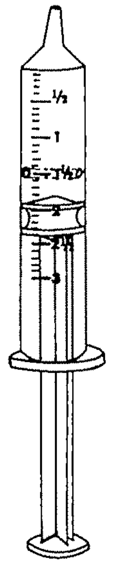

Figure 1. Pulsator blood gas syringe with the 16-gauge needle at the 1.5-mL mark.

Using a 3-mL pulsator blood gas syringe, the plunger is withdrawn and a 16-gauge needle is used to pierce two holes through the cylinder of the syringe at the 1.5-mL mark (Figure 1). The 16-gauge needle is then removed. These holes will permit balloon inflation with 1.5 mL of air, but will prevent overinflation as there will be an air leak above the 1.5-mL mark. Because this is a closed system, sepsis is not a concern. Like the original syringe, this one will also allow passive deflation rather than active deflation, which may cause balloon rupture.

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Book Reviews

Final Approach

John J. Nance. New York: Ballantine, 1990, 407 pp, $4.99.

I often wait for airplanes and I like to read "airport novels." I have never submitted book reviews on them before.

A Boeing 737 is waiting "short of the runway," i.e., next for takeoff, awaiting the landing of an Airbus 320 jumbo jet, which smashes into the 737 broadside. Severe thunderstorms and lightning had prompted the waiting pilot to advise, minutes earlier, to both the tower and the incoming Airbus, that there might be dreaded windshear and that perhaps the Airbus (both were from the same company) ought not to attempt landing. The 737 pilot is rewarded with radioed pilot jargon meaning "butt out" from the Airbus pilot. Recently, the *Wall Street Journal* published an article about several senior corporate (nonairline) executives who were fired for intimidation and for creating an atmosphere in the workplace that was nonconducive to the making of valid contributions by professionals who are subordinates.

Final Approach was written by John Nance, a former airline captain and aviation safety expert. It is, on one level, a skillfully crafted "thriller" novel (yes with a love interest for the protagonist, with more than token feminism). On this level, it is about the investigation of the crash by the National Transportation Safety Board (NTSB), which is charged with determining the cause and making recommendations to the FAA vis à vis possible changes in safety procedures or inspections.

On a different level, this novel opened my eyes to an innovative way of thinking about fear/intimidation/dogma/domination in the workplace by someone designated (either by fate, custom, or self) to be CAPTAIN. Nance elegantly crafts the point that the copilot is *also a professional*. Safety-related advice, suggestions, and information from that individual can only add to the total margin of safety. The "captain" must create the kind of atmosphere wherein all professionals who work in the same workplace are encouraged to think, innovate, be watchful, and contribute. To be sure, the captain is still the final decision maker, but must ask for input, acknowledge it, accept it when it makes sense to do so, and *give credit* to team members who contribute. It is even more difficult to create an atmosphere in which a "copilot" will be empowered to "take control" when it becomes obvious, in the copilot's best professional judgment, that the captain is impaired and unable to perform with competence. According to Nance, this is incredibly difficult to get across to airline captains. Airlines publicly tread lightly on the issue, but they *are* tackling it. They call it "cockpit resource management." Turns out that such an atmosphere of intimidation and fear had been created by the captain of the Airbus that . . . well I won't tell you the rest. Suffice it to say that action by the copilot 0.7 seconds sooner would have . . . there I go—I said I wouldn't tell you any more about the novel!

Everyone who works in operating rooms (the British still insist on calling them "theatres"), where surgery (according to the media) is "performed," understands what I'm talking about here. The novel aspect of Nance's point of view is the idea that if a professional is intimidated, or shuts down to a level where he/she merely follows orders, then that professional has *voluntarily abdicated his/her critical mandate to maximize all possible margins of patient safety*.

Do we discipline people for abusive, intimidative, fear-engendering behavior in operating rooms? Seldom. There are documented extreme cases, some involving actual physical violence and real endangerment, which were not followed by remotely valid discipline to the perpetrators. I have fought against this for many years, long before I read Nance's *Final Approach*, but I did so mostly out of a well-formed sense of fair play. W. Edwards Deming, the American who is revered as a demigod in Japanese industry, taught as one of his now-famous 14 points: "drive out fear." *Final Approach* is not about anesthesia and is not written by an anesthesiologist, but it *is* about one of our most pervasive, perfidious, insidious, even deadly problems. It is time we began to understand the real effects of intimidation and domination of professionals on patient safety in the operating room. Perhaps *Final Approach* will stimulate thinking. Thinking about it and talking among ourselves isn't enough. Again to use another of Deming's points, we need to "take action."

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Anesthesiology Review

R. J. Faust, R. F. Cucchiara, L. N. Milde, S. H. Rose, and T. N. Spackman, eds. New York: Churchill-Livingstone, 1991, 535 pp, $37.95.

As residents approach the end of the academic year, they seek a convenient review method for the American Board of Anesthesiologists' (ABA's) written examination. *Anesthesiology Review*, edited by Ronald J. Faust and colleagues of the Mayo Medical School's Department of Anesthesiology, is a new review book that is designed as a study aid for the ABA's examination. Its aim is to "fill the gap" between the ABA's "content outline" for the written examination and the standard textbooks in the field. *Anesthesiology Review* addresses examination preparation by concentrating on topics listed in the "content outline" and the "key words list." The "key words list" is a list of topics answered incorrectly on the in-service examination that is sent to

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residency program directors and examinees after the examination has been graded. Thus, *Anesthesiology Review* is essentially a "key words" answer book with each chapter covering a topic from the "key word list" provided by the ABA.

The book's organization closely follows the ABA's "content outline." It is divided into three parts: Physiological Sciences, Physical Sciences, and Clinical Sciences. Each part is further divided into sections that are composed of brief, one- to three-page chapters. Each chapter highlights a specific topic that originates from the "key word list." The chapters emphasize the most important points of each topic. They often contain helpful figures, tables, and outlines. In addition, most chapters cite references and contain a short list of suggested readings from major anesthesiology texts.

If the reader is not reviewing topics for the examination, the organization is unsettling because many related topics are spread over several sections of the book and some topics are divided into several separate chapters. For example, with respect to the topic of the hepatobiliary system, the section Physiology contains two chapters that deal with the liver: "Mechanisms of Hepatic Drug Metabolism and Excretion" and "Hepatic Physiology and Preoperative Evaluation." The second section contains two additional chapters that deal with this system: "Hepatic Effects of the Inhalation Agents" and "Narcotic Induced Right-Upper Quadrant Pain," and a subsequent section contains chapters covering anesthesia for patients with hepatocellular disease and acute and chronic alcoholism and anesthesia. While reading about a given topic, I often found myself thinking about issues and problems that were addressed in an entirely different section of the book.

Despite this confusing method of organization, many of the individual chapters follow a format that serves to speed review, aid in comprehension, and enhance memorization and recall of the material. Most chapters have a hybrid mixed format that consists of brief introductory paragraphs followed by either an outline or by paragraphs in which important words or phrases are highlighted. In addition, figures, tables, and diagrams are used where appropriate. This format is effective in providing a succinct review of the essential material. A majority of the chapters follow this mixed format, but some of the chapters are all prose. The prose format is easier to read, but less suited for review and study. Other chapters consist of a group of tables, outlines, and figures that are connected by a few sentences of text. I found those chapters to be unappealing because they are too skeletonized and difficult to read. The editors' failure to enforce a consistent format has resulted in a collection of chapters that vary in format, layout, and quality of presentation. It is unfortunate that the mixed format was not adopted as a standard chapter format because it is so effective and well suited to a review book.

Most of the chapters were written by residents and fellows in training at the Mayo Medical School's Department of Anesthesiology. Some of their chapters were superb, demonstrating a fresh approach to the material, but others lacked inspiration. The remaining chapters were written by well-established authors from the anesthesiology literature. In general, their chapters provided a more consistent presentation. Also, many of the strengths of Mayo's department are reflected in the content of the book. For example, most of the sections that cover neurologic or pulmonary considerations in anesthesia are excellent.

There are two appendices at the end of the book. One is a reprint of the ABA and ASA *Content Outline for In-Training Examinations*. This is a useful study aid because it helps focus the student's attention on the most important issues and topics. It is quite convenient to have this attached to the review book. There is also a "user-friendly" index at the back of the book that indicates topics and makes special notation of tables and figures.

In summary, *Anesthesiology Review* is a useful review of selected topics and a helpful and efficient study aid for the ABA's written examination. It does not (nor do the editors intend it) to replace the existing and established anesthesiology texts. It is an excellent comprehensive review book for the ABA's written examination, and I recommend it to my colleagues who are studying for "the boards" this spring.

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Atlas of Regional Anesthesia

David L. Brown. Philadelphia: W.B. Saunders, 1992, 320 pp, $95.00.

This is certainly a beautifully illustrated book covering a wide number of regional anesthetic techniques that would be useful for both acute and chronic situations. The book is unusual in that there are a number of cross-sectional anatomic illustrations that enable a three-dimensional concept of the anatomy to be visualized and hence the approach to be easily understood. A variety of techniques are offered for most blocks, and at the end of every chapter is found a useful section—"pearls" (personal tips and advice from the author).

Considering David Brown's experience, it might have been helpful to have extended chapter 1 to cover the pros and cons of available equipment. Other regrets were the absence of newer techniques such as cross-section echocardiography and indwelling catheters. Diagrams failed to illustrate the best position of the anesthetist's hands and where to stand (although this was explained in words). The anatomy descriptions were well written, but one often had to turn the page to find the relevant illustration, which detracted from the visual image.

This is probably not an essential personal book but well worth having for those interested in expanding their regional techniques. They will find it easy to use.

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Myofascial Pain and Dysfunction, The Trigger Point Manual, Volume 2: The Lower Extremities

J. G. Travell and D. G. Simons. Baltimore: Williams & Wilkins, 1992, 607 pp, $93.00.

Pain that is persistent beyond the 2–6-week period of injury and inflammatory responses associated with tissue trauma or systemic illness coincides with hypersensitivity either at the neurovascular junction (sympathetically maintained pain) or at the myoneural junction (myofascial pain syndrome). In the realm of multidisciplinary pain management, anesthesiologists frequently serve as diagnosticians, using their expertise to advise patients regarding further physical and psychological rehabilitative therapy. Injections of local anesthetic are often used to identify the somatic correlates of a chronic pain syndrome. A systematic approach to individual diagnosis is based first on history and physical examination. Sympathetically maintained pain (such as reflex sympathetic dystrophy) begins distally in an inflamed, immobile extremity, and is attributed to altered norepinephrine sensitivity at the neurovascular junction. Pain that spreads from the trunk outward (such as low back pain, with or without leg pain) is more likely associated with localized acetylcholine hypersensitivity at the myoneural junction. Low back pain may be the most common complaint of patients referred to an anesthesiologist for diagnosis and recommendations regarding further pain management. Usually pain in these patients is associated with palpable "trigger points" within weight-bearing muscles on the painful side. Presently, there is no systemic medication that results in localized desensitization to acetylcholine at the myoneural junction; but repeated needling of the most sensitive points can produce muscle bundle relaxation. When needling techniques are combined with proper and repeated stretching exercises, ultimate resolution of chronic pain and muscle dysfunction can occur.

The second volume of *Myofascial Pain and Dysfunction, The Trigger Point Manual* specifically addresses posttraumatic myofascial pain syndromes that originate in the low back and that may also involve the lower extremities. After an introductory Pain Guide, which is designed to allow the practitioner to skim quickly muscle groups for trigger points, chapters are sequentially arranged by myotomal segment, beginning at T-12 with the quadratus lumborum. Organization of material within each chapter is clear and consistent, beginning with a description of the pain complaint, patient examination, and trigger point identification. Techniques for injection and specific stretching exercises are included for each involved muscle. Once trigger points are identified and inactivated, a search for the inciting causes of the pain and dysfunction can begin. Reactivators of localized myoneural hypersensitivity can include biochemical disturbances, emotional stressors, chronic posture adaptations (particularly in the workplace), musculoskeletal imbalance, and chronic nerve root swelling or dysfunction. Unless individual reactivators are addressed and resolved, pain-related disability will continue. Accordingly, each chapter contains specific descriptions of posture, activities, and exercise that may reactivate individual trigger points, as well as suggestions for therapeutic approaches to patient management. Although anesthesiologists are unlikely to become involved in all phases of rehabilitation, an understanding of the process is mandatory when reviewing each patient's progress.

As a guide to the diagnosis and management of posttraumatic pain syndromes, *Myofascial Pain and Dysfunction, The Trigger Point Manual, Volume 2: The Lower Extremities* is a book no anesthesiologist involved in the diagnosis and management of patients with chronic back (and leg) pain can afford to be without. Volume 2 was published in 1992, and can be purchased in a two-volume set with the 1983 Volume 1, which describes myofascial pain syndromes of the neck, chest, and abdomen.

Wilhelmina C. Korevaar, MD
Hospital of the University of Pennsylvania
Philadelphia, Pennsylvania

Books Received

Receipt of the books listed below is acknowledged. Selected books from this list will be reviewed in future issues of the Journal.

The Journal solicits reviews of new books from its readers. If you wish to submit a review, before proceeding please send a letter of intent, identifying the book in question, to Dr. Norig Ellison, Department of Anesthesia, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104. The Journal reserves the right of final decision on publication.

Barash PG, Cullen BF, Stoelting RK, eds. *Clinical Anesthesia*, 2nd ed. Philadelphia: J.B. Lippincott, 1992, 1739 pp, $135.00, ISBN 0-397-51160-4.

Dawson-Saunders B, Trapp RG. *Basic and Clinical Biostatistics*. Norwalk, Connecticut: Appleton & Lange, 1992, 329 pp, $29.95, ISBN 0-8385-6200-0.

Lasagna L, Weintraub M. *Year Book of Drug Therapy 1992*. St. Louis: Mosby Year Book, 1992, 426 pp, $59.95, ISBN 0-8151-4611-6.

Levy JH. *Anaphylactic Reactions in Anesthesia and Intensive Care*, 2nd ed. Stoneham, Massachusetts: Butterworth-Heinemann, 1992, 266 pp, $39.95, ISBN 0-7506-9064-X.

Vender JS, Spiess BD, eds. *Post Anesthesia Care*. Philadelphia: W.B. Saunders, 1992, 400 pp, $45.00, ISBN 0-7216-5648-X.

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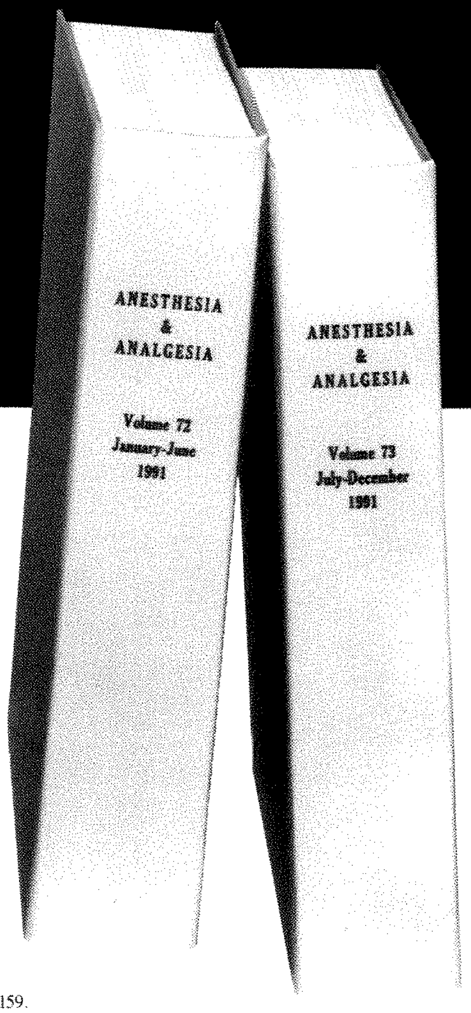

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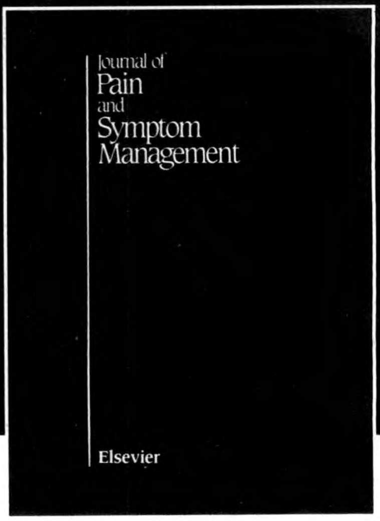
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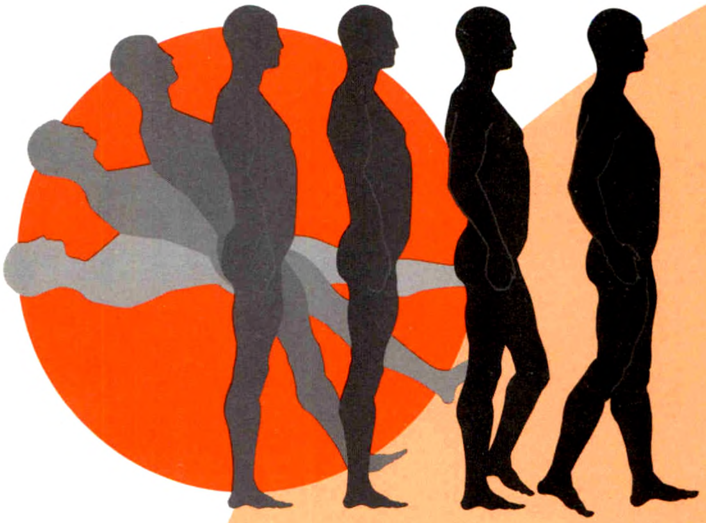


"The duration of action of mivacurium defines a new class of non-depolarizing neuromuscular blocking drugs."p.397

Caldwell JE, Heier T, Kitts JB, Lynam DP, Fahey MR, Miller RD.
Comparison of the neuromuscular block induced by mivacurium,
suxamethonium or atracurium during nitrous oxide-fentanyl anaesthesia.
***Br J Anaesth*. 1989;63:393-399.**

Please see brief summaries for **M**IVACRON® (mivacurium chloride) and Tracrium® (atracurium besylate) following this ad.

MIVACRON®

The first and only shor

Duration of action and spontaneous recovery profile approximately one-third to one-half that of intermediate agents such as atracurium or vecuronium

Initial dose 0.15 mg/kg

Profound neuromuscular block

Recommended initial adult dose

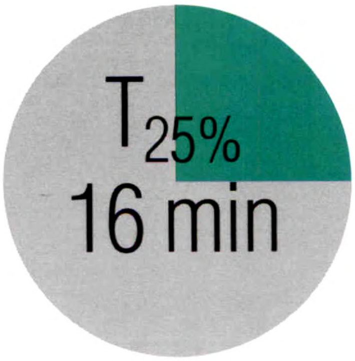
The recommended initial adult bolus dose of 0.15 mg/kg (administered over 5 to 15 seconds) provides profound neuromuscular block.

Intubation 2.5 min

Generally good to excellent intubating conditions

Useful for routine intubation

MIVACRON provides generally good to excellent intubating conditions in 2.5 minutes at a dose of 0.15 mg/kg. Succinylcholine remains the drug of choice for rapid sequence intubation.



Short duration of action

Well-suited for short procedures

Duration of clinically effective block (time to 25% recovery of T_1) following injection of 0.15 mg/kg is 16 minutes, making **M**IVACRON excellent for short procedures.[1]

from Burroughs Wellcome Co.

acting nondepolarizer

Reduce spontaneous recovery time by up to 50% *vs* vecuronium

	Duration of continuous infusion (min)	Recovery times (min) Off-25%*	25-75%	5-95%
MIVACRON (n=25)	**86.2±5.6**	**5.7±0.3**	**6.4±0.2**	**13.6±0.6**
vecuronium (n=18)	96.8±6.6	12.7±1.3[†]	13.8±0.9[‡]	32.0±1.2[‡§]
atracurium (n=22)	91.3±2.9	12.5±0.6[†]	10.9±0.3[†]	26.6±0.4[†]

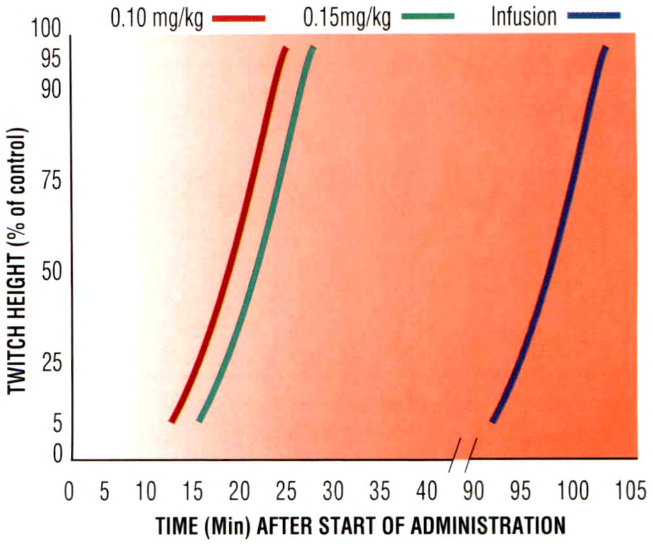
Adapted from Ali et al, p. 544.[2] *Time from discontinuation of infusion to 25% recovery. [†]P<0.01 atracurium or vecuronium vs **M**IVACRON; [‡]P<0.001 vecuronium vs **M**IVACRON; [§]P<0.05 vecuronium vs atracurium.

Noncumulative

Continuous infusion of **M**IVACRON for up to 2.5 hours is not associated with the development of tachyphylaxis or cumulative neuromuscular blocking effects in ASA Physical Status I-II patients. Steady-state levels of block are rapidly achieved with minimal adjustment to the infusion rate. Limited data are available on **M**IVACRON (a mixture of three isomers) for infusions longer than 2.5 hours.

Savarese et al found...

Fast recovery following bolus or infusion



Adapted from Savarese et al, p. 727.[3]

MIVACRON® Injection 2 mg/mL

(mivacurium chloride)

Short duration, fast recovery

Please see brief summaries for **M**IVACRON® (mivacurium chloride) and Tracrium® (atracurium besylate) following this ad.

MIVACRON®

Up to half the duration

Excellent cardiovascular profile at recommended doses

MIVACRON Initial Dose* (mg/kg)	% of patients with ≥30% change			
	MAP		HR	
	↓	↑	↓	↑
0.07 to 0.10	0%	2%	0%	0%
0.15	4%	4%	4%	2%
0.20†	30%	0%	0%	8%
0.25†	39%	2%	0%	14%

*During opioid/N_2O/O_2 anesthesia.

†Experimental dose, in excess of the maximum recommended dose of 0.15 mg/kg.

Minimal CV effects

At the recommended initial dose of 0.15 mg/kg, cardiovascular response to **M**IVACRON is minimal. Higher doses may produce effects associated with histamine release and may result in a decrease in blood pressure in some individuals. The incidence and magnitude of these hemodynamic changes are related to size of the dose and speed of the injection. In patients with clinically significant CV disease, the initial dose of **M**IVACRON should be administered over 60 seconds.

Metabolized by plasma cholinesterase

Like succinylcholine, **M**IVACRON should be used with caution in patients with reduced plasma cholinesterase activity. In patients heterozygous for the atypical plasma cholinesterase gene, clinically effective duration may be prolonged by approximately 10 minutes. Homozygous patients (1 in 2500) are *extremely sensitive* to **M**IVACRON. **M**IVACRON should be used with great caution, if at all, in homozygous patients.

However, unlike succinylcholine, once recovery has begun, **M**IVACRON can be reversed with conventional doses of neostigmine.

Individualization of dosages

- Significant CV disease
- Obesity
- Renal or hepatic disease
- History suggesting greater sensitivity to release of histamine or related mediators

from Burroughs Wellcome Co.

half the recovery time

A nondepolarizing alternative to succinylcholine for elective outpatient surgery

	n	Time to max. block (min)*	Time to recovery of T_1=10% (min)*
succinylcholine 1.0 mg/kg	9	1.1±0.2	7.7±1.4
MIVACRON 0.15 mg/kg	8	**2.5**±0.9	**15.6**±3.4

Adapted from Caldwell et al, p.395.[1] *P<0.05 succinylcholine vs **M**IVACRON.

Caldwell et al concluded...

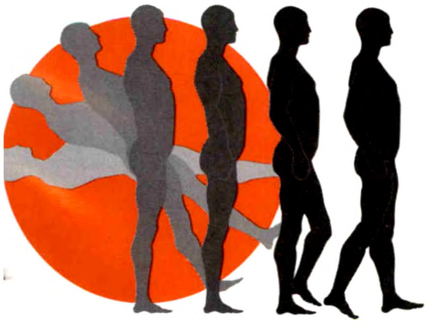
"...in those clinical situations in which rapid onset of action is not required, mivacurium is an alternative to [succinylcholine] for production of profound neuromuscular block of short duration." p.398

Plus...

- For use by bolus or infusion
- Ready-to-use solution
- Room temperature storage
- Available in 5 mL and 10 mL vials (2 mg/mL) and 50 mL premixed infusion bags (0.5 mg/mL)

REFERENCES

1.Caldwell JE, Heier T, Kitts JB, Lynam DP, Fahey MR, Miller RD. Comparison of the neuromuscular block induced by mivacurium, suxamethonium or atracurium during nitrous oxide-fentanyl anaesthesia. *Br J Anaesth.* 1989;63:393-399.
2. Ali HH, Savarese JJ, Embree PB, et al. Clinical pharmacology of mivacurium chloride (BW B1090U) infusion: comparison with vecuronium and atracurium. *Br J Anaesth.* 1988;61:541-546.
3. Savarese JJ, Ali HH, Basta SJ, et al. The clinical neuromuscular pharmacology of mivacurium chloride (BW B1090U): a short-acting nondepolarizing ester neuromuscular blocking drug. *Anesthesiology.* 1988;68:723-732.



MIVACRON® Injection 2 mg/mL
(mivacurium chloride)
Short duration, fast recovery

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MIVACRON® INJECTION
MIVACRON® PREMIXED INFUSION
(MIVACURIUM CHLORIDE)

Brief Summary

This drug should be administered only by adequately trained individuals familiar with its actions, characteristics, and hazards.

INDICATIONS AND USAGE: MIVACRON is a short-acting neuromuscular blocking agent indicated for inpatients and outpatients, as an adjunct to general anesthesia, to facilitate tracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

CONTRAINDICATIONS: MIVACRON is contraindicated in patients known to have an allergic hypersensitivity to mivacurium chloride or other benzylisoquinolinium agents, as manifested by reactions such as urticaria or severe respiratory distress or hypotension. Use of MIVACRON from multidose vials is contraindicated in patients with a known allergy to benzyl alcohol.

WARNINGS: MIVACRON SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH THE DRUG'S ACTIONS AND THE POSSIBLE COMPLICATIONS OF ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS PERSONNEL AND FACILITIES FOR RESUSCITATION AND LIFE SUPPORT (TRACHEAL INTUBATION, ARTIFICIAL VENTILATION, OXYGEN THERAPY), AND AN ANTAGONIST OF MIVACRON ARE IMMEDIATELY AVAILABLE. IT IS RECOMMENDED THAT A PERIPHERAL NERVE STIMULATOR BE USED TO MEASURE NEUROMUSCULAR FUNCTION DURING THE ADMINISTRATION OF MIVACRON IN ORDER TO MONITOR DRUG EFFECT, DETERMINE THE NEED FOR ADDITIONAL DRUG, AND CONFIRM RECOVERY FROM NEUROMUSCULAR BLOCK.

MIVACRON HAS NO KNOWN EFFECT ON CONSCIOUSNESS, PAIN THRESHOLD, OR CEREBRATION. TO AVOID DISTRESS TO THE PATIENT, NEUROMUSCULAR BLOCK SHOULD NOT BE INDUCED BEFORE UNCONSCIOUSNESS.

MIVACRON IS METABOLIZED BY PLASMA CHOLINESTERASE AND SHOULD BE USED WITH GREAT CAUTION, IF AT ALL, IN PATIENTS KNOWN TO BE OR SUSPECTED OF BEING HOMOZYGOUS FOR THE ATYPICAL PLASMA CHOLINESTERASE GENE.

MIVACRON Injection and MIVACRON Premixed Infusion are acidic (pH 3.5 to 5.0) and may not be compatible with alkaline solutions having a pH greater than 8.5 (*e.g.*, barbiturate solutions).

PRECAUTIONS:

General: Although MIVACRON (a mixture of three stereoisomers) is not a potent histamine releaser, the possibility of substantial histamine release must be considered. Release of histamine is related to the dose and speed of injection.

Caution should be exercised in administering MIVACRON to patients with clinically significant cardiovascular disease and patients with any history suggesting a greater sensitivity to the release of histamine or related mediators (*e.g.*, asthma). In such patients, the initial dose of MIVACRON should be 0.15 mg/kg or less, administered over 60 seconds; assurance of adequate hydration and careful monitoring of hemodynamic status are important (see **Hemodynamics** and **Individualization of Dosages** subsections of CLINICAL PHARMACOLOGY).

Obese patients may be more likely to experience clinically significant transient decreases in MAP than non-obese patients when the dose of MIVACRON is based on actual rather than ideal body weight. Therefore, in obese patients, the initial dose should be determined using the patient's ideal body weight (see **Hemodynamics** and **Individualization of Dosages** subsections of CLINICAL PHARMACOLOGY).

Recommended doses of MIVACRON have no clinically significant effects on heart rate; therefore, MIVACRON will not counteract the bradycardia produced by many anesthetic agents or by vagal stimulation.

Neuromuscular blocking agents may have a profound effect in patients with neuromuscular diseases (*e.g.*, myasthenia gravis and the myasthenic syndrome). In these and other conditions in which prolonged neuromuscular block is a possibility (*e.g.*, carcinomatosis), the use of a peripheral nerve stimulator and a dose of not more than 0.015–0.020 mg/kg MIVACRON is recommended to assess the level of neuromuscular block and to monitor dosage requirements (see **Individualization of Dosages** subsection of CLINICAL PHARMACOLOGY).

MIVACRON has not been studied in patients with burns. Resistance to nondepolarizing neuromuscular blocking agents may develop in patients with burns, depending upon the time elapsed since the injury and the size of the burn. Patients with burns may have reduced plasma cholinesterase activity which may offset this resistance (see **Individualization of Dosages** subsection of CLINICAL PHARMACOLOGY).

Acid-base and/or serum electrolyte abnormalities may potentiate or antagonize the action of neuromuscular blocking agents. The action of neuromuscular blocking agents may be enhanced by magnesium salts administered for the management of toxemia of pregnancy (see **Individualization of Dosages** subsection of CLINICAL PHARMACOLOGY).

No data are available to support the use of MIVACRON by intramuscular injection.

Renal and Hepatic Disease: The possibility of prolonged neuromuscular block must be considered when MIVACRON is used in patients with renal or hepatic disease (see **Pharmacokinetics** subsection of CLINICAL PHARMACOLOGY). Most patients with chronic hepatic disease such as hepatitis, liver abscess, and cirrhosis of the liver exhibit a marked reduction in plasma cholinesterase activity. Patients with acute or chronic renal disease may also show a reduction in plasma cholinesterase activity (see **Individualization of Dosages** subsection of CLINICAL PHARMACOLOGY).

Reduced Plasma Cholinesterase Activity: The possibility of prolonged neuromuscular block following administration of MIVACRON must be considered in patients with reduced plasma cholinesterase (pseudocholinesterase) activity.

Plasma cholinesterase activity may be diminished in the presence of genetic abnormalities of plasma cholinesterase (*e.g.*, patients heterozygous or homozygous for the atypical plasma cholinesterase gene), pregnancy, liver or kidney disease, malignant tumors, infections, burns, anemia, decompensated heart disease, peptic ulcer, or myxedema. Plasma cholinesterase activity may also be diminished by chronic administration of oral contraceptives, glucocorticoids, or certain monoamine oxidase inhibitors and by irreversible inhibitors of plasma cholinesterase (*e.g.*, organophosphate insecticides, echothiophate, and certain antineoplastic drugs).

MIVACRON has been used safely in patients heterozygous for the atypical plasma cholinesterase gene. At doses of 0.10 to 0.20 mg/kg MIVACRON, the clinically effective duration of action was 8 to 11 minutes longer in patients heterozygous for the atypical gene than in genotypically normal patients.

As with succinylcholine, patients homozygous for the atypical plasma cholinesterase gene (1 in 2500 patients) are extremely sensitive to the neuromuscular blocking effect of MIVACRON. In three such adult patients, a small dose of 0.03 mg/kg (approximately the $ED_{10\text{-}20}$ in genotypically normal patients) produced complete neuromuscular block for 26 to 128 minutes. Once spontaneous recovery had begun, neuromuscular block in these patients was antagonized with conventional doses of neostigmine. One adult patient, who was homozygous for the atypical plasma cholinesterase gene, received a dose of 0.18 mg/kg MIVACRON and exhibited complete neuromuscular block for about 4 hours. Response to post-tetanic stimulation was present after 4 hours, all four responses to train-of-four stimulation were present after 6 hours, and the patient was extubated after 8 hour Reversal was not attempted in this patient.

Malignant Hyperthermia (MH): In a study of MH-susceptible pigs, MIVACRON did not trigger MI MIVACRON has not been studied in MH-susceptible patients. Because MH can develop in the absen of established triggering agents, the clinician should be prepared to recognize and treat MH in ar patient undergoing general anesthesia.

Long-Term Use in the Intensive Care Unit (ICU): No data are available on the long-term use MIVACRON in patients undergoing mechanical ventilation in the ICU.

Drug Interactions: Although MIVACRON (a mixture of three stereoisomers) has been administere safely following succinylcholine-facilitated tracheal intubation, the interaction between the stereois mers in MIVACRON and succinylcholine has not been systematically studied. Prior administrati of succinylcholine can potentiate the neuromuscular blocking effects of nondepolarizing agents. Eviden of spontaneous recovery from succinylcholine should be observed before the administration MIVACRON.

The use of MIVACRON before succinylcholine to attenuate some of the side effects of succinylcholin has not been studied.

There are no clinical data on the use of MIVACRON with other nondepolarizing neuromuscular bloc ing agents.

Isoflurane and enflurane (administered with nitrous oxide/oxygen to achieve 1.25 MAC) decreas the ED_{50} of MIVACRON by as much as 25% (see **Pharmacodynamics** and **Individualization** **Dosages** subsections of CLINICAL PHARMACOLOGY). These agents may also prolong the cli ically effective duration of action and decrease the average infusion requirement of MIVACRON as much as 35% to 40%. A greater potentiation of the neuromuscular blocking effects of th stereoisomers in MIVACRON may be expected with higher concentrations of enflurane or isofluran Halothane has little or no effect on the ED_{50}, but may prolong the duration of action and decreas the average infusion requirement by as much as 20%.

Other drugs which may enhance the neuromuscular blocking action of nondepolarizing agents suc as the stereoisomers in MIVACRON include certain antibiotics (*e.g.*, aminoglycosides, tetracycline bacitracin, polymyxins, lincomycin, clindamycin, colistin, and sodium colistimethate), magnesiu salts, lithium, local anesthetics, procainamide, and quinidine. Drugs that may enhance the neur muscular blocking effects of mivacurium by a reduction in plasma cholinesterase activity include chro ic administration of oral contraceptives, glucocorticoids, or certain monoamine oxidase inhibito and by irreversible inhibitors of plasma cholinesterase (see **Reduced Plasma Cholinesterase Activit** subsection of PRECAUTIONS).

Resistance to the neuromuscular blocking action of nondepolarizing neuromuscular blockin agents has been demonstrated in patients chronically administered phenytoin or carbamazepin While the effects of chronic phenytoin or carbamazepine therapy on the action of the stereoisomer in MIVACRON are unknown, slightly shorter durations of neuromuscular block may be anticipate and infusion rate requirements may be higher.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis and fertility studie have not been performed. MIVACRON was evaluated in a battery of four short-term mutagenici tests. It was non-mutagenic in the Ames Salmonella assay, the mouse lymphoma assay, th human lymphocyte assay, and the *in vivo* rat bone marrow cytogenetic assay.

Pregnancy: *Teratogenic Effects:* Pregnancy Category C. Teratology testing in nonventilate pregnant rats and mice treated subcutaneously with maximum subparalyzing doses of MIVACRO revealed no maternal or fetal toxicity or teratogenic effects. There are no adequate and wel controlled studies of MIVACRON in pregnant women. Because animal studies are not always pr dictive of human response, and the doses used were subparalyzing, MIVACRON should be use during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: The use of MIVACRON during labor, vaginal delivery, or cesarean section h not been studied in humans and it is not known whether MIVACRON administered to the mother h effects on the fetus. Doses of 0.08 and 0.20 mg/kg MIVACRON given to female beagles undergoi cesarean section resulted in negligible levels of the stereoisomers in MIVACRON in umbilical ve sel blood of neonates and no deleterious effects on the puppies.

Nursing Mothers: It is not known whether any of the stereoisomers of mivacurium are excreted human milk. Because many drugs are excreted in human milk, caution should be exercised followi administration of MIVACRON to a nursing woman.

Pediatric Use: MIVACRON has not been studied in children below the age of 2 years (see CLI ICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION for clinical experience and re ommendations for use in children 2 to 12 years of age).

Geriatric Use: MIVACRON was safely administered during clinical trials to 64 elderly (≥65 year patients, including 31 patients with significant cardiovascular disease (see **General** subsection PRECAUTIONS). The duration of neuromuscular block may be slightly longer in elderly patients th in young adult patients (see CLINICAL PHARMACOLOGY).

ADVERSE REACTIONS:

Observed in Clinical Trials: MIVACRON (a mixture of three stereoisomers) was well tolerated d ing extensive clinical trials in inpatients and outpatients. Prolonged neuromuscular block, which an important adverse experience associated with neuromuscular blocking agents as a class, w reported as an adverse experience in 3 of 2074 patients administered MIVACRON. The most co monly reported adverse experience following the administration of MIVACRON was transie dose-dependent cutaneous flushing about the face, neck, and/or chest. Flushing was most frequen noted after the initial dose of MIVACRON and was reported in about 20% of adult patients who receiv the recommended dose of 0.15 mg/kg MIVACRON over 5 to 15 seconds. When present, flushi typically began within 1 to 2 minutes after the dose of MIVACRON and lasted for 3 to 5 minutes. 60 patients who experienced flushing after 0.15 mg/kg MIVACRON, one patient also experienc mild hypotension that was not treated, and one patient experienced moderate wheezing that w successfully treated.

Overall, hypotension was infrequently reported as an adverse experience in the clinical trials MIVACRON. None of the 397 adults or 63 children who received recommended doses was treat for a decrease in blood pressure associated with the administration of MIVACRON. Above the re ommended dosage range, 1% to 2% of healthy adults given ≥0.20 mg/kg over 5 to 15 seconds a 2% to 4% of cardiac surgery patients given ≥0.20 mg/kg over 60 seconds were treated f decreases in blood pressure associated with the administration of MIVACRON.

The following adverse experiences were reported in patients administered MIVACRON (all even judged by investigators during the clinical trials to have a possible causal relationship):

Incidence Greater Than 1% -

Cardiovascular:	Flushing (15%)

Incidence Less Than 1% -

Cardiovascular:	Hypotension, Tachycardia, Bradycardia, Cardiac Arrhythmia, Phlebiti
Respiratory:	Bronchospasm, Wheezing, Hypoxemia
Dermatological:	Rash, Urticaria, Erythema, Injection Site Reaction
Nonspecific:	Prolonged Drug Effect
Neurologic:	Dizziness
Musculoskeletal:	Muscle Spasms

OVERDOSAGE: Overdosage with neuromuscular blocking agents may result in neuromuscular blo beyond the time needed for surgery and anesthesia. The primary treatment is maintenance of a pate airway and controlled ventilation until recovery of normal neuromuscular function is assured. Once evidence of recovery from neuromuscular block is observed, further recovery may be facilitated by administration of an anticholinesterase agent (*e.g.*, neostigmine, edrophonium) in conjunction with an appropriate anticholinergic agent. (see **Antagonism of Neuromuscular Block**). Overdosage may increase the risk of hemodynamic side effects, especially decreases in blood pressure. If needed, cardiovascular support may be provided by proper positioning of the patient, fluid administration, and/or vasopressor agent administration.

Antagonism of Neuromuscular Block:

ANTAGONISTS (SUCH AS NEOSTIGMINE) SHOULD NOT BE ADMINISTERED WHEN COMPLETE NEUROMUSCULAR BLOCK IS EVIDENT OR SUSPECTED. THE USE OF A PERIPHERAL NERVE STIMULATOR TO EVALUATE RECOVERY AND ANTAGONISM OF NEUROMUSCULAR BLOCK IS RECOMMENDED.

Administration of 0.030 to 0.064 mg/kg neostigmine or 0.5 mg/kg edrophonium at approximately 10% recovery from neuromuscular block (range: 1 to 15) produced 95% recovery of the muscle twitch response and a T_4/T_1 ratio ≥75% in about 10 minutes. The times from 25% recovery of the muscle twitch response to T_4/T_1 ratio ≥75% following these doses of antagonists averaged about 7 to 9 minutes. In comparison, average times for spontaneous recovery from 25% to T_4/T_1 ≥75% were 12 to 13 minutes.

Patients administered antagonists should be evaluated for adequate clinical evidence of antagonism, *e.g.*, 5-second head lift and grip strength. Ventilation must be supported until no longer required. Antagonism may be delayed in the presence of debilitation, carcinomatosis, and the concomitant use of certain broad spectrum antibiotics, or anesthetic agents and other drugs which enhance neuromuscular block or separately cause respiratory depression (see **Drug Interactions** subsection of PRECAUTIONS). Under such circumstances the management is the same as that of prolonged neuromuscular block (see OVERDOSAGE).

DOSAGE AND ADMINISTRATION: MIVACRON SHOULD ONLY BE ADMINISTERED INTRAVENOUSLY.

The dosage information provided below is intended as a guide only. Doses of MIVACRON should be individualized (see **Individualization of Dosages** subsection of CLINICAL PHARMACOLOGY). Factors that may warrant dosage adjustment include but may not be limited to: the presence of significant kidney, liver, or cardiovascular disease, obesity (patients weighing ≥30% more than ideal body weight for height), asthma, reduction in plasma cholinesterase activity, and the presence of inhalational anesthetic agents. The use of a peripheral nerve stimulator will permit the most advantageous use of MIVACRON, minimize the possibility of overdosage or underdosage, and assist in the evaluation of recovery.

Adults:

Initial Doses:

A dose of 0.15 mg/kg MIVACRON administered over 5 to 15 seconds is recommended for facilitation of tracheal intubation for most patients. When administered as a component of a thiopental/opioid/nitrous oxide/oxygen induction-intubation technique, 0.15 mg/kg (2 x ED_{95}) MIVACRON produces generally good-to-excellent conditions for tracheal intubation in 2.5 minutes. Lower doses of MIVACRON may result in a longer time for development of satisfactory intubation conditions. Administration of MIVACRON doses above the recommended range (≥0.20 mg/kg) is associated with the development of transient decreases in blood pressure in some patients (see CLINICAL PHARMACOLOGY and ADVERSE REACTIONS).

STORAGE: Store MIVACRON Injection at room temperature of 15° to 25°C (59° to 77°F). Avoid exposure to direct ultraviolet light. DO NOT FREEZE.

Recommended storage for MIVACRON Premixed Infusion is room temperature (15° to 25°C/59° to 77°F). Avoid excessive heat. Avoid exposure to direct ultraviolet light. Protect from freezing.

U.S. Patent No. 4761418

BURROUGHS WELLCOME CO.
Research Triangle Park, NC 27709

MIVACRON Premixed Infusion
Manufactured for
BURROUGHS WELLCOME CO.
by Abbott Laboratories
North Chicago, IL 60064

06-4814
Printed in U.S.A. January 1992 670002

TRACRIUM® INJECTION

(atracurium besylate)

Brief Summary

This drug should be used only by adequately trained individuals familiar with its actions, characteristics, and hazards.

INDICATIONS AND USAGE: Tracrium is indicated, as an adjunct to general anesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

CONTRAINDICATIONS: Tracrium is contraindicated in patients known to have a hypersensitivity to it.

WARNINGS: TRACRIUM SHOULD BE USED ONLY BY THOSE SKILLED IN AIRWAY MANAGEMENT AND RESPIRATORY SUPPORT. EQUIPMENT AND PERSONNEL MUST BE IMMEDIATELY AVAILABLE FOR ENDOTRACHEAL INTUBATION AND SUPPORT OF VENTILATION, INCLUDING ADMINISTRATION OF POSITIVE PRESSURE OXYGEN. ADEQUACY OF RESPIRATION MUST BE ASSURED THROUGH ASSISTED OR CONTROLLED VENTILATION. ANTICHOLINESTERASE REVERSAL AGENTS SHOULD BE IMMEDIATELY AVAILABLE. DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION. Tracrium has no known effect on consciousness, pain threshold, or cerebration. It should be used only with adequate anesthesia. Tracrium Injection, which has an acid pH, should not be mixed with alkaline solutions (e.g., barbiturate solutions) in the same syringe or administered simultaneously during intravenous infusion through the same needle. Depending on the resultant pH of such mixtures, Tracrium may be inactivated and a free acid may be precipitated. Tracrium Injection 10 mL multiple dose vials contain benzyl alcohol. Benzyl alcohol has been associated with an increased incidence of neurological and other complications in newborn infants which are sometimes fatal. Tracrium Injection 5 mL single use vials do not contain benzyl alcohol.

PRECAUTIONS: General: Although Tracrium is a less potent histamine releaser than d-tubocurarine or metocurine, the possibility of substantial histamine release in sensitive individuals must be considered. Special caution should be exercised in administering Tracrium to patients in whom substantial histamine release would be especially hazardous (e.g., patients with clinically significant cardiovascular disease) and in patients with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release. In these patients, the recommended initial Tracrium dose is lower (0.3 to 0.4 mg/kg) than for other patients and should be administered slowly or in divided doses over one minute. Since Tracrium has no clinically significant effects on heart rate in the recommended dosage range, it will not counteract the bradycardia produced by many anesthetic agents or vagal stimulation. As a result, bradycardia during anesthesia may be more common with Tracrium than with other muscle relaxants. Tracrium may have profound effects in patients with myasthenia gravis, Eaton-Lambert syndrome, or other neuromuscular diseases in which potentiation of nondepolarizing agents has been noted. The use of a peripheral nerve stimulator is especially important for assessing neuromuscular blockade in these patients. Similar precautions should be taken in patients with severe electrolyte disorders or carcinomatosis. Multiple factors in anesthesia practice are suspected of triggering malignant hyperthermia (MH), a potentially fatal hypermetabolic state of skeletal muscle. Halogenated anesthetic agents and succinylcholine are recognized as the principal pharmacologic triggering agents in MH-susceptible patients; however, since MH can develop in the absence of established triggering agents, the clinician should be prepared to recognize and treat MH in any patient scheduled for general anesthesia. Reports of MH have been rare in cases in which Tracrium has been used. In studies of MH-susceptible animals (swine) and in a clinical study of MH-susceptible patients, Tracrium did not trigger this syndrome. Resistance to nondepolarizing neuromuscular blocking agents may develop in burn patients. Increased doses of nondepolarizing muscle relaxants may be required in burn patients and are dependent on the time elapsed since the burn injury and the size of the burn. The safety of Tracrium has not been established in patients with bronchial asthma. **Long-Term Use in Intensive Care Unit (ICU):** Tracrium has been used to facilitate mechanical ventilation in ICU patients. When there is a need for long-term mechanical ventilation, the benefits to risk ratio of neuromuscular blockade must be considered. There is only limited information on the efficacy and safety of Tracrium administered by long-term (days to weeks) intravenous infusion to facilitate mechanical ventilation in intensive care facilities. For Tracrium, as with other neuromuscular blocking agents used in intensive care facilities, available evidence suggests that there is wide interpatient variability in dosage requirements and that these requirements may change with time. Limited data suggest that Tracrium infusion requirements may increase with prolonged administration in the ICU. As with other neuromuscular blocking agents, little information is available on the plasma levels or clinical consequences of atracurium metabolites following long-term (days to weeks) infusion of Tracrium in the intensive care unit setting. One metabolite of atracurium, laudanosine, when administered alone to laboratory animals, has been associated with cerebral excitatory effects. Physiological effects of laudanosine in humans have not been demonstrated. The effects of hemodialysis, hemoperfusion and hemofiltration on plasma levels of atracurium and its metabolites are unknown. **Drug Interactions:** Drugs which may enhance neuromuscular blocking action of Tracrium include: enflurane; isoflurane; halothane; certain antibiotics, especially the aminoglycosides and polymyxins; lithium; magnesium salts; procainamide; and quinidine. If other muscle relaxants are used during the same procedure, the possibility of a synergistic or antagonist effect should be considered. The prior administration of succinylcholine does not enhance the duration, but quickens the onset and may increase the depth, of neuromuscular blockade induced by Tracrium. Tracrium should not be administered until a patient has recovered from succinylcholine-induced neuromuscular blockade. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** A positive response was observed in the mouse lymphoma assay under conditions which killed over 80% of the treated cells. A far weaker response was observed in the presence of metabolic activation at concentrations which also killed over 80% of the treated cells. **Pregnancy:** ***Teratogenic Effects:*** Pregnancy Category C. Tracrium has been shown to be potentially teratogenic in rabbits, when given in doses up to approximately one-half the human dose. There are no adequate and well-controlled studies in pregnant women. Tracrium should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Labor and Delivery:** It is not known whether muscle relaxants administered during vaginal delivery have immediate or delayed adverse effects on the fetus or increase the likelihood that resuscitation of the newborn will be necessary. The possibility that forceps delivery will be necessary may increase. Tracrium (0.3 mg/kg) has been administered to 26 pregnant women during delivery by cesarean section. No harmful effects were attributable to Tracrium in any of the newborn infants, although small amounts of Tracrium were shown to cross the placental barrier. The possibility of respiratory depression in the newborn infant should always be considered following cesarean section during which a neuromuscular blocking agent has been administered. In patients receiving magnesium sulfate, the reversal of neuromuscular blockade may be unsatisfactory and Tracrium dose should be lowered as indicated. **Nursing Mothers:** It is not known whether this drug is excreted in human milk. Caution should be exercised when Tracrium is administered to a nursing woman. **Pediatric Use:** Safety and effectiveness in children below the age of 1 month have not been established.

ADVERSE REACTIONS: Observed in Controlled Clinical Studies: Tracrium produced few adverse reactions during extensive clinical trials. Most were suggestive of histamine release (see Precautions Section). The overall incidence rate for clinically important adverse reactions was 7/875 or 0.8%. Most adverse reactions were of little clinical significance unless they were associated with significant hemodynamic changes. Substantial vital sign changes greater than or equal to 30% observed in 530 patients, without cardiovascular disease, were as follows: in those patients given the recommended initial dosage range of 0.31 to 0.50 mg/kg of Tracrium, mean arterial pressure increased in 2.8% and decreased in 2.1% of patients while the heart rate increased in 2.8% of these patients. At doses of ≥ 0.60 mg/kg, 14.3% of the studied patients had a decrease in mean arterial pressure while 4.8% had an increase in heart rate. At doses ≤ 0.30 mg/kg, mean arterial pressure increased in 1.9% and decreased in 1.1% of patients, while heart rate increased in 1.6% and decreased in 0.8% of these patients. **Observed in Clinical Practice:** Based on clinical experience in the U.S. and the United Kingdom of approximately 3 million patients given Tracrium the following adverse reactions are among the most frequently reported: *General:* allergic reactions (anaphylactic or anaphylactoid) which, in rare instances, were severe (e.g., cardiac arrest); *Musculoskeletal:* inadequate, prolonged block; *Cardiovascular:* hypotension, vasodilatation (flushing), tachycardia, bradycardia; *Respiratory:* dyspnea, bronchospasm, laryngospasm; *Integumentary:* rash, urticaria, injection site reaction.

STORAGE: Tracrium Injection should be refrigerated at 2° to 8° C (36° to 46° F) to preserve potency. DO NOT FREEZE. Upon removal from refrigeration to room temperature storage conditions (25°C/77°F), use Tracrium Injection within 14 days even if rerefrigerated.

U.S. Patent No. 4179507 December 1990 627248

Burroughs Wellcome Co., Research Triangle Park, North Carolina 27709

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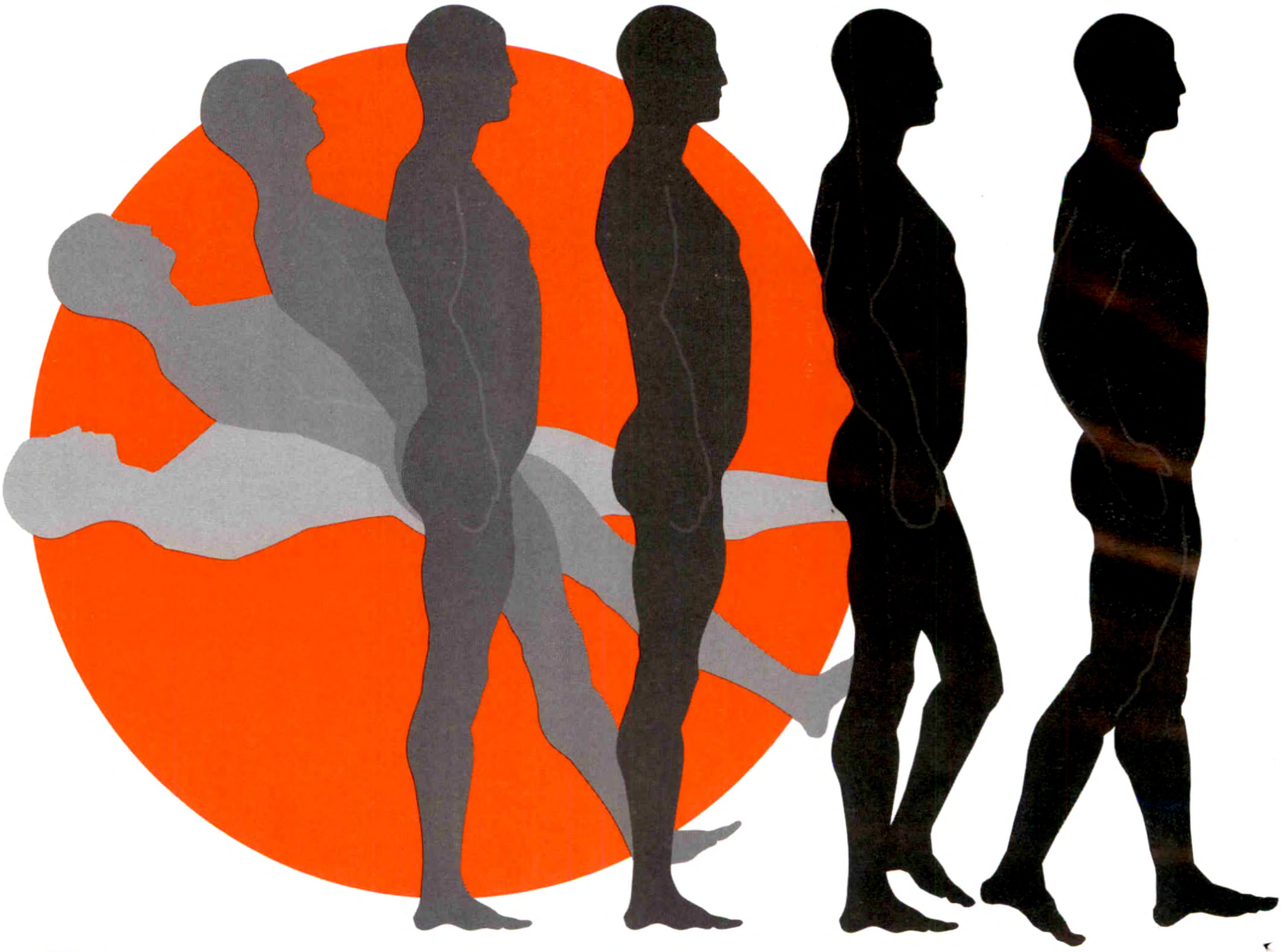

Short duration, fast recovery

MIVACRON® Injection 2 mg/mL
(mivacurium chloride)

Please see brief summaries for **MIVACRON**® (mivacurium chloride) and Tracrium® (atracurium besylate) on preceding pages.

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Classified Advertising

OHIO
Anesthesiologist, University Hospitals. Must be at least board eligible. Equal Opportunity, Affirmative Action Employer. Send curriculum vitae to Helmut F. Cascorbi, MD, PhD, Professor and Chairman, Department of Anesthesiology, University Hospitals of Cleveland, 2074 Abington Road, Cleveland, OH 44106.

701E/L

ILLINOIS: ANESTHESIOLOGIST
To join congenial group of MDs/CRNAs expanding to provide anesthesia coverage for only hospital in city since recent merger. No open heart or neurosurgery. Environment conducive to family living, variety of schools, recreation. Good opportunity with stable future. City located in east central Illinois with population of approximately 40,000 (35-mile radius service area with 126,126 population). Within driving distance of Chicago and Indianapolis. Please send CV to Box 887D/L.

887D/L

EASTERN PENNSYLVANIA
Hospital needs two board-certified/board-eligible anesthesiologists to join a fee-for-service group in a 225-bed progressive hospital. Applicants must be a PGIV preferrably with pain management, residency rotation. Reply to Box 888D/I.

888D/I

CARDIOVASCULAR FELLOWSHIP OPPORTUNITY
The Department of Anesthesiology and Critical Care Medicine at the University of New Mexico School of Medicine has openings at the CA-4 level for advanced training in cardiovascular anesthesiology. The fellowship is a 2-year comprehensive program designed to train the fellow for a career in cardiovascular anesthesiology. Research in cardiovascular physiology and anesthesia, provision of clinical care for complex adult and pediatric cases, participation in conference, and teaching responsibilities are part of the fellowship experience. Interested individuals should send CV or contact Jorge A. Estrin, MD, PhD, Professor and Chairman, Department of Anesthesiology, University of New Mexico School of Medicine, Albuquerque, NM 83131-5216, (505) 272-2610, FAX (505) 277-1300. The University of New Mexico is an Equal Opportunity/Affirmative Action Employer.

912F/L

THE UNIVERSITY OF NEW MEXICO
Department of Anesthesiology and Critical Care Medicine has immediate faculty positions at the Instructor, Assistant Professor, Associate Professor, and Professor levels for candidates with experience in cardiac, obstetric, neurosurgical, and pediatric anesthesia and critical care medicine. Responsibilities include the teaching of medical students and residents and the provision of clinical care in a busy tertiary referral center. Opportunities to pursue research interests will be provided. It is expected that candidates who apply for CCM positions will have or be eligible for subspecialty certification. Qualified candidates should send CV or contact Jorge A. Estrin, MD, PhD, Professor and Chairman, Department of Anesthesiology, University of New Mexico School of Medicine, Albuquerque, NM 87131-5216, (505) 272-2610, FAX (505) 277-1300. The University of New Mexico is an Equal Opportunity/Affirmative Action Employer.

913F/L

Immediate opening for a BC/BE anesthesiologist to join six MD anesthesiologists in a fee-for-service practice in a 350-bed hospital in a retirement community in Sun City, Arizona. No OB, open heart, trauma, or pediatrics. Send replies to Box 923GHI.

923GHI

NORTH EAST, INDIANA
Group seeking BC/BE anesthesiologists to join large MD-only group. All types of anesthesia provided, including OH and OB. Immediate opening. Early partnership offered. Send CV to Box 926G/I.

926G/I

The Department of Anesthesiology at Duke University Medical Center invites qualified full-time faculty to apply for positions in the following categories: NEUROANESTHESIA—We are seeking an academic faculty candidate trained in neurosurgical anesthesia to lead a developing neuroanesthesia section as chief of the section. This opportunity requires a candidate with a primary interest in investigative research and teaching in addition to clinical expertise in all aspects of neuroanesthesiology including an interest in the development of a neurological intensive care unit. A new spacious neuroscience facility at Duke fosters interdisciplinary relationships with neuropharmacology, neuroradiology, neurobiology, and neurology. The neuroscience program at Duke University is one of the five developing centers of excellence at this nationally prominent university. CRITICAL CARE MEDICINE—We are seeking individuals who are ABA certified or board eligible in critical care medicine, for the position of Co-Director, SICU at the Durham VA Medical Center (where a new ICU tower is under construction) and/or as critical care faculty in the SICU at Duke University Medical Center. Faculty will play an essential role in the coordination of care in a multidisciplinary consulting service and in the development of an interdisciplinary Critical Care Fellowship program. GENERAL INTERESTS AND CLINICAL PHARMACOLOGY—We have positions for starting academicians whose subspecialty interests are broad or undefined, but who desire to begin an academic career in a setting with an emphasis on clinical research in pharmacology and epidemiology as it relates to the practice of anesthesiology.

Academic titles and compensation for the

CLASSIFIED ADS

Anesthesia & Analgesia makes available classified advertising space for those interested in obtaining positions or wishing to announce meetings, postgraduate courses, or other pertinent events. We require that all advertisements be relevant to the practice of anesthesia and analgesia, and we reserve the right to refuse advertisements that are not relevant.

Specifications. Ads should be typewritten on letterhead stationery; the text should be double-spaced, with the title or key phrase typed in capital letters. Enclose two photocopies with each ad. Display space (minimum ¼ page) is available through Pharmaceutical Media, Inc., 440 Park Avenue South, 14th floor, New York, NY 10016, telephone: (212) 685-5010, FAX: (212) 685-6126.

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Deadline. Copy must be received 7 weeks before publication date (i.e., by January 1 for the March issue); multiple-insertion ads are welcome. Ads may run up to 6 months per purchase order/payment. Please specify in which issue(s) your advertisement is to appear.

Send all ad copy, payments, and correspondence to: *Anesthesia & Analgesia*, Classified Ads, Desk Editorial, Elsevier Science Publishing Co., Inc., 655 Avenue of the Americas, New York, NY 10010.

*When responding to a box number ad, include the box number on all correspondence.

above positions will be commensurate with experience and credentials in education, clinical service, and research. Candidates must be board certified or board eligible, and eligible for an unrestricted North Carolina medical license. Please send letter of application and curriculum vitae to J. G. Reves, MD, Box 3094, Duke University Medical Center, Durham, NC 27710. Duke University is an Affirmative Action-Equal Opportunity Employer.

927G/I

LAKE CHAMPLAIN-ADIRONDACK REGION NEW YORK

Growing group seeks a BC/BE anesthesiologist at 410-bed regional referral hospital. Department consists of six anesthesiologists and two CRNAs for 6000 cases/year. No hearts or transplants. Mostly Narkomed 3 machines with H-P Merlin monitors. Plattsburgh is located at the foothills of the Adirondacks and on Lake Champlain, the sixth largest lake in the country. Montreal and Lake Placid region are within 1-hour drive. Excellent public and private schools, state university, affordable real estate, active arts council, and wide variety of recreational activities combine to offer an extraordinary family environment. For details or to view a video of the hospital and community, contact Hannah Hanford, Box 1656, Plattsburgh, NY 12901; (518) 643-2998.

929G/I

CALIFORNIA

University of California, Irvine: Openings for faculty positions in the Department of Anesthesiology. (1) Assistant or associate professor level in the in-residence series. Responsibilities include teaching and research. (2) Clinical instructor and assistant professor level in the clinical series. Responsibilities include teaching and clinical service. Participation in research is highly desirable but not mandatory

Rank and pay commensurate with skills and experience. Faculty will serve at both a tertiary-care university hospital and a VA Medical Center. Candidates must be ABA certified, or in the examination process, and be eligible for a California state license. An Affirmative Action, Equal Opportunity Employer. Address correspondence with references and curriculum vitae to Steven J. Barker, PhD, MD, Chair, Department of Anesthesiology, University of California, Irvine Medical Center, 101 City Drive South, Route 81A, Orange, CA 92668.

930G/L

LOUISIANA STATE UNIVERSITY MEDICAL CENTER—SHREVEPORT

Faculty positions available for board certified/eligible anesthesiologists. Duties include patient care, resident and student teaching, supervision of CRNAs, research, and administrative responsibilities. Faculty rank and salary commensurate with experience. Please send curriculum vitae and names of three references to D. Richard Davis, II, MD, Associate Professor and Chairman, Department of Anesthesiology, LSU Medical Center—Shreveport, 1501 Kings Highway, Shreveport, LA 71130-3932. We are an Equal Opportunity/Affirmative Action Employer.

931G/L

TENNESSEE

Expanding department requires additional anesthesiologists. Full-time positions available at levels of instructor to associate professor with emphasis on teaching, patient care, and clinical research. Prerequisites: (1) meet Tennessee license requirements; (2) ABA diplomat or eligible for ABA examination. All subspecialties needed. Excellent opportunity for anesthesiologists who want an ideal mix of private practice with teaching and clinical research. Send curriculum vitae, bibliography, and the names and addresses of three references to John Zanella, Jr, MD, PhD, Professor and Chairman, Department of Anesthesiology, University of Tennessee, Memphis, 800 Madison Avenue, Memphis, TN 38163. The University of Tennessee is an Equal Opportunity Employer/Affirmative Action Register/Title IX/Section 504 Employer.

934H/J

ANESTHESIOLOGIST

Multispecialty group of 43 physicians adjacent to 165-bed hospital in need of BC/BE anesthesiologist. Located in West Texas City of 80,000 with excellent recreational activities. Salary guarantee with bonus based on production. Send CV to West Texas Medical Associates, 3555 Knickerbocker Road, San Angelo, TX 76904.

936H/A

NEW ORLEANS

Louisiana State University Medical Center, Department of Anesthesiology, is seeking a board-certified anesthesiologist who is interested in directing publications and research. Outstanding opportunities for clinical studies are available. No night call, weekends, or holidays are required. Excellent salary and fringe benefits. Eligibility for Louisiana licensure is prerequisite. Please send curriculum vitae to M. Naraghi, MD, Professor and Chairman, LSU Department of Anesthesiology, 1532 Tulane Avenue, New Orleans, LA 70140. LSUMC is an EEO/AA employer.

937H/A

OLEAN, N.Y.

Anesthesiologist to join expanding group serving busy hospital in the beautiful Southern Tier. Very competitive salary and benefits. School loans may be forgiven. Send CV to Joseph Kehoe, RR 1, Box 363, Clayton, NY 13624 or call (315) 686-2434 for details.

940H/J

CARDIAC ANESTHESIOLOGIST

Albert Einstein Medical Center is a 600-bed, university-affiliated, tertiary-care hospital with a rapidly growing cardiac surgical program. The Division of Cardiac Anesthesia seeks BC/BE individuals who have completed a cardiac fellowship or have significant cardiac experience. The position includes clinical care and teaching responsibilities. Rank and salary commensurate with experience. Send curriculum vitae to Rick Fine, MD, Chairman, Division of Cardiac Anesthesia, Albert Einstein Medical Center, 5501 Old York Road, Philadelphia, PA 19141-3098.

941HI

ILLINOIS

Opening for full or part-time BC/BE anesthesiologist to join group practice with academic affiliation. Eleven physicians and 15 CRNAs, cardiothoracic, neuro, neonatal, and OB. Excellent salary and benefits. Send CV to Sangamon Anesthesiologists, St. John's Hospital, 800 East Carpenter, Springfield, IL 62769. (217) 544-3311 (collect).

942H/J

ANESTHESIOLOGIST — BC/BE — Immediate opening. All specialties including cardiac. Excellent salary leading to early partnership. Send CV to Medical Associates, PO Box 141, Minot, ND 58702. (701) 857-5448; FAX (701) 839-8024.

943H/J

TEXAS

Private practice group is seeking BE/BC anesthesiologist(s) to join new group forming in North Central Texas just minutes from the Dallas/Ft. Worth Metroplex. Excellent starting salary and practice opportunity. Also accepting applications from CRNAs seeking employment. Facility is a 200-bed community hospital involving predominantly orthopedics, general, and ENT cases with obstetrical service starting immediately. Send CV to NTAA, P.O. Box 630652, Iriving, TX 75063-0652.

945HI

PENNSYLVANIA

The ALBERT EINSTEIN MEDICAL CENTER has two faculty positions available. (1) PAIN: To spend 40% of time in pain clinic and additional time on the acute postoperative pain service. Possibility for appointment as Co-Director of Pain Medicine for the right individual. For the individual with special interest in upper extremity regional blockade, there is an opportunity to work with two new hand surgeons. (2) PEDIATRIC: To become a member of a four-person pediatric anesthesia team. About 20% of time will be pediatrics.

For both positions, clinical responsibility is for all types of predominantly adult cases except cardiac. Interest in teaching residents required; interest in research preferred.

The Albert Einstein Medical Center is a modern 600+ bed tertiary hospital, level one trauma center, and a transplant center in Philadelphia. Over 12,000 anesthetics performed annually. All faculty (18) receive full academic appointments at the Temple University School of Medicine. Very competitive salary and benefits. Interested applicants should reply with CV to Jonathan Roth, MD, Department of Anesthesiology, Albert Einstein Medical Center, 5501 Old York Road, Philadelphia, PA 19141. (215) 456-7979.

946HI

MEMORIAL SLOAN-KETTERING CANCER CENTER

Postgraduate Course on "Current Concepts in Cancer and Acute Pain Management," December 10–11, 1992. This course will provide a broad coverage of the management of cancer pain and acute pain for the practicing anesthesiologist. The objective is to exchange information on recent advances, current concepts in diagnosis, and the technical advancement in pain management.

HIGHLIGHTS: State-of-the-art lectures, syllabus, CME credit in Category I.

REGISTRATION: $350.00 for physicians before October 1, 1992; $400.00 for physicians from October 2 to December 9, 1992; $450.00 for ON-SITE registration; $250.00 for 1-day attendance; $200.00 for residents,* fellows,* and nurses (with letter from Program Director*). For more details, please contact: CME office, MSKCC, 1275 York Avenue, New York, NY 10021. (212) 639-6754, (212) 717-3140 FAX.

947HI

PAIN MANAGEMENT TRAINING—ACUTE AND CHRONIC—CA-3 AND FELLOWSHIP POSITIONS

University of Cincinnati Anesthesia Department and the Pain Control Center are seeking applications for Fellowship (preferred) and CA-3 positions in acute and chronic pain management, including cancer pain and pediatric pain management. Chronic benign pain is managed in an interdisciplinary fashion, run by anesthesiologists; program includes inpatient, intensive outpatient, and standard outpatient programs. The Acute Pain Service is aggressive and well accepted, employing all modalities in the management of postoperative and ICU/trauma patients. Opportunities are available for clinical research. Direct inquiries to Donna Benesch, Department of Anesthesia, University of Cincinnati Medical Center, 231 Bethesda Avenue, ML 531, Cincinnati, OH 45267-0531. Phone: (513) 558-6356, FAX: (513) 558-0995.

948H/J

POSTDOCTORAL FELLOWSHIP

Background in clinical medicine or clinical research required for studies with patients with heart disease undergoing surgery. Cardiac function and ischemia assessed with ECG, Holter, and echocardiography monitoring. Working with cardiologists, epidemiologists, and anesthesiologists. Send CV and names of three references to Dennis T. Mangano, PhD, MD, Professor and Vice Chairman, Department of Anesthesia, University of California, San Francisco, 4150 Clement Street (129), San Francisco, CA 94121.

949H/L

FELLOWSHIPS

The Department of Anesthesiology at the University of Alabama at Birmingham offers fellowships for 1–2 years with a 50% to 80% commitment to clinical or bench research with the remaining 20% to 50% commitment to clinical training. Fellowships are available without a research commitment. The fellowships are available in the following areas: (1) *Cardiothoracic Anesthesia*, (2) *Pain Management* (including chronic pain, postoperative pain, pain management of patients with terminal cancer), (3) *Transplantation* (including renal, hepatic, pancreatic, cardiac, and lung), (4) *Neuroanesthesia* (including brain and spinal cord electrophysiological monitoring), (5) *Outpatient Anesthesia*, (6) *Obstetrics*, (7) *Laboratory Research* (pain mechanisms, ischemia-reperfusion injury, nitric oxide, and others). Please send curriculum vitae to Simon Gelman, MD, PhD, Professor and Chairman, Department of Anesthesiology, University of Alabama at Birmingham, 619 South 19th Street, Birmingham AL 35233. An Affirmative Action/Equal Employment Opportunity Employer.

950H/J

CHIEF—CRITICAL CARE DIVISION, ASSOCIATE DIRECTOR—SURGICAL ICU

Department of Anesthesiology, University of Alabama at Birmingham is seeking a board-certified anesthesiologist, certified or eligible in critical care medicine, for Chief—Division of Critical Care and Associate Director—Surgical ICU. Responsibilities include subspecialty resident education in critical care, patient care, research, administration, and recruitment of anesthesiologists-intensivists. Excellent research opportunities. Highly competitive salaries. Contact Simon Gelman, MD, PhD, Professor and Chairman, Department of Anesthesiology, University of Alabama at Birmingham, 619 South 19th Street, Birmingham, AL 35233, (205) 934-4696. An Affirmative Action/Equal Employment Opportunity Employer.

951H/J

CA-IV POSITIONS IN ANESTHESIOLOGY

The Department of Anesthesia at New England Medical Center Hospitals, Boston, Massachusetts (Tufts University) is accepting applications for CA-IV positions in adult cardiac anesthesia. This will be a 6–12-month rotation specializing in all aspects of cardiac anesthesia. Include CV with letter. Reply to Box 952HI.

952HI

OB anesthesiologist sought for large university-affiliated hospital. Approximate 300 deliveries a month with many high risk. In-house neonatologists. Reasonable call schedule with competitive compensation package and partnership after 1 year. Send or fax CV to Barney S. H. Feinstein, MD, Chairman, Department of Anesthesia, Washington Hospital Center, 110 Irving Street, NW, Washington, DC 20010; Fax number (202) 877-5564.

872CEGIK

BC/BE anesthesiologist for a 500-bed tertiary hospital in a Florida coastal city. Immediate opening. Liberal salary and early partnership. Send resume to Box 956I/L.

956I/L

Pain fellowship available for 12 months of formal training beginning January 1, 1993 or July 1993. Multidisciplinary chronic pain service treating a wide spectrum of conditions. Active acute pain service; strong emphasis on regional anesthesia. Excellent hands-on experience; research projects available if desired. Please send CV to Sanford L. Klein, DDS, MD, Chairman, Department of Anesthesia, UMDNJ-Robert Wood Johnson Medical School, 1 Robert Wood Johnson Place, CN 19, New Brunswick, NJ 08903-0019. UMDNJ, NJ's university of the health sciences, is an Affirmative Action/Equal Employment Opportunity Employer, m/f/h/v, and a member of the University Health System of New Jersey.

953IA

Anesthesiologist, DO, board-certified, 25 years' experience, licensed in WA, MI, PA, and MO, presently chairman of 7-man department in general medical hospital, interested in making a change. Reply to Box 954I.

954I

UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL SCHOOL OF MEDICINE, ANESTHESIOLOGY DEPARTMENT, is seeking qualified applicants for clinical and tenure-track faculty positions. Demonstrated experience in a subspecialty clinical area (e.g., Pain Management, Obstetric, Critical Care Medicine, etc.), teaching experience, emerging research productivity, and proven ability to present research at major medical meetings are desirable. Women and minorities are encouraged to voluntarily identify themselves. Applicants should send a curriculum vitae, a short statement of academic goals, and three letters of reference to Edward Norfleet, MD, Chairman, Anesthesiology Faculty Search Committee, Department of Anesthesiology, CB #7010, 223 Burnett-Womack, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599-7010. The University of North Carolina at Chapel Hill is an Affirmative Action/Equal Opportunity Employer.

955I

BOISE, IDAHO—PAIN MANAGEMENT

MD/CRNA group seeking additional BC/BE anesthesiologist with pain fellowship or extensive pain experience for expanding pain clinic. Growing 250-bed hospital soon to be adding a Cancer Institute and Open Heart program. No OB. Great opportunity in progressive community (130,000) located in the foothills. Excellent for family and all types of year-round recreation. Partnership after 1 year. Please respond to William G. Binegar, MD, 6054 Emerald, Boise, ID 83704-8863.

957I/K

COASTAL NEW JERSEY—ANESTHESIOLOGIST DESIRED

Immediate opening for BC or BE MD/DO to join an expanding group practice of 10 MDAs and 9 CRNAs covering a 500-bed regional medical center composed of two hospitals performing over 9000 anesthetics. All types of anesthesia except OH. Great opportunity for energetic well-trained individual. Unlimited opportunity and outstanding lifestyle in a family-oriented seashore community. Very competitive financial package. Please reply with CV to S. Hernberg, DO, Chairman, Department of Anesthesiology, 1925 Pacific Avenue, Atlantic City, NJ 08401.

958I/K

Anesthesiologist to join group consisting of eight anesthesiologists and two CRNAs. Must be board eligible or board certified. Established PC with many fringe benefits in effect. Send CV to Associated Anesthesiologists of Saginaw, PC, 3121 Davenport, Saginaw, MI 48602 or call (517) 791-2150.

959I/K

ANESTHESIOLOGIST—ST. LOUIS

Diversified Anesthesia Services, Inc., a thriving St. Louis based anesthesia group is seeking a BC/BE anesthesiologist to join the group. We offer an excellent financial package leading to partnership after 2 years. Direct inquiries and curriculum vitae to Sidney Bennett, MD, Department of Anesthesiology, Third Floor, Deaconess Hospital, 6150 Oakland Avenue, St. Louis, MO 63139; (314) 768-3198.

960I

PENNSYLVANIA

Faculty positions are available for board certified or eligible anesthesiologists at the University of Pittsburgh Medical Center. Position level and salary are dependent upon qualifications, with responsibilities including clinical care, teaching, and various aspects of administration and research. EEO/AA Employer. Send credentials to Peter M. Winter, MD, Chairman, Department of Anesthesiology, University of Pittsburgh Medical Center, A-1305 Scaife Hall, Pittsburgh, PA 15261.

961I

WANTED

TWO ACADEMIC ANESTHESIOLOGISTS at the clinical instructor/clinical assistant professor level. Must have an MD degree, completed a 4-year residency in anesthesiology, have documentation in researh fellowship or postgraduate training, and be board certified or board eligible. The positions have an anticipated starting date of January 4, 1993 or later in the academic year. Stipend negotiable and dependent on credentials. Interested parties should forward letter including board status, curriculum vitae, and bibliography to Robert E. Redfern, MD, Search Committee Chairman, Department of Anesthesiology, University of Florida Health Science Center Jacksonville, 655 West 8th Street, Jacksonville, FL 32209. Application recruiting deadline for both positions is October 15, 1992. Equal Employment Opportunity/Affirmative Action Employer.

964I

PHILADELPHIA, PA.

BC/BE anesthesiologist to join physician/CRNA group in a private, university-affiliated, center-city, tertiary-care hospital. No obstetrics, trauma, or pediatrics. Fellowship experience in open heart anesthesia required. Competitive salary, benefits, and potential for partnership is included. Respond with CV to Box 965I/K.

965I/K

DIRECTORSHIP: VIRGINIA BEACH, VIRGINIA

Opportunity for an anesthesiologist with experience in ambulatory surgery to direct a new ambulatory surgery center in coastal Virginia. Join a group of eight anesthesiologists as Medical Director. No call and/no weekends. Salary plus bonus with exceptional benefits/pension plan. Send CV, or call Greg Pilgrim, Jackson and Coker, Inc., 115 Perimeter Center Place, Suite 380 12187, Atlanta, GA 30346; telephone: 1-800-544-1987.

966I

UCSF PEDIATRIC ANESTHESIOLOGY FELLOWSHIP

The Departments of Anesthesia at the University of California, San Francisco and Children's Hospital of Northern California, Oakland, California are jointly offering two 1-year clinical fellowship positions (CA-4) in pediatric anesthesiology beginning *July 1993*. The fellowship will include extensive operating room experience in all pediatric subspecialties in both institutions and critical care medicine exposure for both neonates, older infants, and children. The fellows will spend 6 months in each institution. Send inquiries to Dolores Scholz, Postdoctoral Coordinator, Department of Anesthesia, University of California, San Francisco, Box 0648, San Francisco, CA 94143-0648.

967I/L

ANESTHESIOLOGIST

Department of Anesthesiology at the SUNY Health Science Center in Syracuse, N.Y. is recruiting faculty at the instructor and assistant and associate professor levels. Qualified individuals with a strong academic commitment in all types of anesthesia, critical care, and pain management are sought. SUNY Health Science Center is a tertiary-care center and provides clinical services also to the Syracuse Veterans Administration Hospital. Rank and salary are commensurate with experience. Must be board certified or board eligible and possess a New York State medical license. Please send letter, curriculum vitae, names, addresses, and phone numbers of three references to Enrico M. Camporesi, MD, Professor and Chairman, Department of Anesthesiology, SUNY Health Science Center, Syracuse, NY 13210. The State University of New York Health Science Center is an Equal Opportunity/AA Employer.

968I/K

ANESTHESIOLOGIST/PAIN MANAGEMENT (PORTLAND, OREGON)

Northwest Permanente, P.C., a stable, multispecialty group providing care for 380,000 members of Kaiser Permanente, is seeking a BC/BE anesthesiologist to join a group of 9 anesthesiologists and 27 CRNAs at our 220-bed Sunnyside Medical Center, one of two Kaiser medical centers in the Portland area. Group provides full range of anesthesia services except for open heart.

Special interest: Pain Management, fellowship trained. Join two other trained MDs part-time in a growing Chronic Pain Clinic with dedicated time, clinical procedure-room space, and an OR block for fluoroscopy procedures. The department has ongoing research projects in both pain and anesthesia and is preparing a book manuscript on pain.

Stimulating professional environment, beautiful recreation area with easy access to mountains and beaches. Excellent salary and benefits including paid malpractice, sabbatical, two pension plans, and more. Please forward CV to Fred M. Nomura, MD, Regional Medical Director, NORTHWEST PERMANENTE, P.C., 2701 N.W. Vaughn, Suite 300, Portland, OR 97210-5398. EOE.

969I

UNIVERSARY OF CALIFORNIA, DAVIS—
Assistant Professor/Associate Professor/Full Professor

Department of Anesthesiology, University of California, Davis, Medical Center is recruiting for two (2) faculty positions at all ranks. These positions require experience in teaching and clinical training, as well as clinical research. Both positions require demonstrated experience, training, and certification in (1) Critical Care to join two other faculty covering ICU 2–3 months per year; (2) Transplant; and (3) General Anesthesia. These positions are in the non-tenured track. Rank and salary are commensurate with experience and based on the UCD School of Medicine Faculty Compensation Plan. Must be board certified or board eligible in anesthesiology, and a California medical license is required. Send curriculum vitae, bibliography, copies of publications, and *the names of three (3) references* to: Dennis Fung, MD, Acting Chairman, Department of Anesthesiology, University of California, Davis, 2315 Stockton Boulevard, Room 2304, Sacramento, CA 95817. Positions are open until filled but not later than December 31, 1992. The University of California, Davis is an Equal Opportunity/Affirmative Action Employer with a strong institutional commitment to the achievement of diversity among its faculty and staff. In that spirit, we are particularly interested in receiving applications from persons of under-represented groups, including women, ethnic minorities, disabled veterans, Vietnam-era veterans, and handicapped persons.

970I/K

RESIDENT POSITIONS

Available at all levels in an expanding teaching program in Boston, Massachusetts. Send CV to or contact Ina Gibson, Coordinator, Department of Anesthesiology, St. Elizabeth's Hospital, 736 Cambridge Street, Brighton, MA 02135; (617) 789-2782, FAX (617) 254-6384.

971I

ANESTHESIOLOGISTS—MONTREAL

Board certified/FRCPC. Pediatric academic teaching hospital with all major subspecialties. Guaranteed research time. Interest in pain management and/or cardiovascular anesthesia an advantage. In accordance with Canadian immigration requirements this is directed to Canadian citizens and permanent residents of Canada. McGill University is committed to equity in employment. CV to Dr. D. G. Spence, Director, Montreal Children's Hospital, 2300 Tupper Street, Room C-1118, Montreal, QC, H3H 1P3.

972I

ARKANSAS

Pediatric anesthesia fellowship to begin July 1, 1993. Broad-based training in pediatric anesthesia includes experience in cardiac, pain management, and critical care. Active research program. Prefer applicants who have completed CA-3 level in approved residency program. Must be eligible for Arkansas licensure. Send curriculum vitae to Raeford E. Brown, Jr., MD, Chief, Division of Pediatric Anesthesia, Arkansas Children's Hospital, 800 Marshall Street, Little Rock, AR 72202-3591. An Equal Opportunity Employer.

973I/K

CALIFORNIA

The UCLA Department of Anesthesiology is represented by all anesthesia subspecialties. From time to time faculty positions in the Department become available. Appointment in the CLINICIAN-TEACHER Academic Professorial Series requires clinical and teaching skills, interest or experience in clinical research, eligibility for a California medical license, and ABA certification or in process. Appointment in the REGULAR PROFESSORIAL SERIES (TENURE TRACK) additionally requires evidence of research productivity, scholarly writing, and a commitment to discovery. Appointment as an Associate Professor or Full Professor in either of these academic series requires demonstration that you have been continuously and effectively engaged in creative activity of high quality and significance. Send your inquiry with curriculum vitae and names of five references to Joseph C. Gabel, MD, Department of Anesthesiology, UCLA School of Medicine, Los Angeles, CA 90024-1778. UCLA is an Affirmative Action Equal Opportunity Employer.

974I

PEDIATRIC ANESTHESIOLOGIST

BC/BE fellowship-trained to join private group in southern California. Opportunity exists to head pediatric subsection due to newly established relationship with a local children's hospital. Individual must be proficient and willing to provide care in areas of adult anesthesiology, i.e., OB, trauma, neuro. No cardiac requirements. Call Brian Levine, MD, Mission Anesthesia Medical Associates; (714) 240-6057.

975I

ANESTHESIOLOGIST

AMG, B/C, 8 years' experience. Pediatric fellowship. Current adult experience. Desires F/T same-day surgery or similar. No call. LIC PA, NY, TN, MA. Reply to Box 976I.

976I

DIRECTOR OF OBSTETRIC ANESTHESIOLOGY

The Department of Anesthesiology at the University of Rochester is seeking a Director of Obstetric Anesthesiology, with outstanding qualifications in clinical care, teaching, and research, to assume clinical leadership and to develop advanced education and research programs in obstetric anesthesiology.

Board certification in anesthesiology or its equivalent is required. Academic rank and salary will be commensurate with qualifications. Opportunities for independent or collaborative research are abundant.

Interested candidates should send curriculum vitae to Denham S. Ward, MD, PhD, Professor and Chairman Designate, Department of Anesthesiology, University of Rochester Medical Center, 601 Elmwood Avenue, Rochester, NY 14642. The University of Rochester is an Equal Opportunity Employer.

977IJ

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933H/A

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935HI

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763I/H

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898E/L

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910I

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Impaired Respiration: ALFENTA should be used with caution in patients with pulmonary disease, decreased respiratory reserve or potentially compromised respiration. In such patients, opioids may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration.

Impaired Hepatic or Renal Function: In patients with liver or kidney dysfunction, ALFENTA should be administered with caution due to the importance of these organs in the metabolism and excretion of ALFENTA.

Drug Interactions: Both the magnitude and duration of central nervous system and cardiovascular effects may be enhanced when ALFENTA is administered in combination with other CNS depressants such as barbiturates, tranquilizers, opioids, or inhalation general anesthetics. Postoperative respiratory depression may be enhanced or prolonged by these agents. In such cases of combined treatment, the dose of one or both agents should be reduced. Limited clinical experience indicates that requirements for volatile inhalation anesthetics are reduced by 30 to 50% for the first sixty (60) minutes following ALFENTA induction. The concomitant use of erythromycin with ALFENTA can significantly inhibit ALFENTA clearance and may increase the risk of prolonged or delayed respiratory depression. Perioperative administration of drugs affecting hepatic blood flow or enzyme function may reduce plasma clearance and prolong recovery.

Carcinogenesis, Mutagenesis and Impairment of Fertility: No long-term animal studies of ALFENTA have been performed to evaluate carcinogenic potential. The micronucleus test in female rats and the dominant lethal test in female and male mice revealed that single intravenous doses of ALFENTA as high as 20 mg/kg (approximately 40 times the upper human dose) produced no structural chromosome mutations or induction of dominant lethal mutations. The Ames *Salmonella typhimurium* metabolic activating test also revealed no mutagenic activity.

Pregnancy Category C: ALFENTA has been shown to have an embryocidal effect in rats and rabbits when given in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects could have been due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug. No evidence of teratogenic effects has been observed after administration of ALFENTA in rats or rabbits. There are no adequate and well-controlled studies in pregnant women. ALFENTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: There are insufficient data to support the use of ALFENTA in labor and delivery. Placental transfer of the drug has been reported; therefore, use in labor and delivery is not recommended.

Nursing Mothers: In one study of nine women undergoing post-partum tubal ligation, significant levels of ALFENTA were detected in colostrum four hours after administration of 60 µg/kg of ALFENTA, with no detectable levels present after 28 hours. Caution should be exercised when ALFENTA is administered to a nursing woman.

Pediatric Use: Adequate data to support the use of ALFENTA in children under 12 years of age are not presently available.

ADVERSE REACTIONS: The most common adverse reactions, respiratory depression and skeletal muscle rigidity, are extensions of known pharmacological effects of opioids. See CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS on the management of respiratory depression and skeletal muscle rigidity. Delayed respiratory depression, respiratory arrest, bradycardia, asystole, arrhythmias and hypotension have also been reported. The reported incidences of adverse reactions listed in the following table are derived from controlled and open clinical trials involving 1183 patients, of whom 785 received ALFENTA. The controlled trials involved treatment comparisons with fentanyl, thiopental sodium, enflurane, saline placebo and halothane. Incidences are based on disturbing and nondisturbing adverse reactions reported. The comparative incidence of certain side effects is influenced by the type of use, e.g., chest wall rigidity has a higher reported incidence in clinical trials of alfentanil induction, and by the type of surgery, e.g., nausea and vomiting have a higher incidence in patients undergoing gynecologic surgery.

Percent	ALFENTA (N = 785)	Fentanyl (N = 243)	Thiopental Sodium (N = 66)	Enflurane (N = 55)	Halothane (N = 18)	Saline Placebo* (N = 18)
Gastrointestinal						
Nausea	28	44	14	5	0	22
Vomiting	18	31	11	9	13	17
Cardiovascular						
Bradycardia	14	7	8	0	0	0
Tachycardia	12	12	39	36	31	11
Hypotension	10	8	7	7	0	0
Hypertension	18	13	30	20	6	0
Arrhythmia	2	2	5	4	6	0
Musculoskeletal						
Chest Wall Rigidity	17	12	0	0	0	0
Skeletal Muscle Movements	6	2	6	2	0	0
Respiratory						
Apnea	7	0	0	0	0	0
Postoperative Respiratory Depression	2	2	0	0	0	0
CNS						
Dizziness	3	5	0	0	0	0
Sleepiness/ Postoperative Sedation	2	8	2	0	0	6
Blurred Vision	2	2	0	0	0	0

*From two clinical trials, one involving supplemented balanced barbiturate / nitrous oxide anesthesia and one in healthy volunteers who did not undergo surgery.

In addition, other adverse reactions less frequently reported (1% or less) were: Laryngospasm, bronchospasm, postoperative confusion, headache, shivering, postoperative euphoria, hypercarbia, pain on injection, urticaria, and itching. Some degree of skeletal muscle rigidity should be expected with induction doses of ALFENTA.

DRUG ABUSE AND DEPENDENCE: ALFENTA (alfentanil hydrochloride) is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and therefore has the potential for being abused.

OVERDOSAGE: Overdosage would be manifested by extension of the pharmacological actions of ALFENTA (alfentanil hydrochloride) (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. No experience of overdosage with ALFENTA was reported during clinical trials. The intravenous LD_{50} of ALFENTA is 43.0-50.9 mg/kg in rats, 72.2-73.6 mg/kg in mice, 71.8-81.9 mg/kg in guinea pigs and 59.5-87.5 mg/kg in dogs. Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression. The duration of respiratory depression following overdosage with ALFENTA may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist should not preclude immediate establishment of a patent airway, administration of oxygen, and assisted or controlled ventilation as indicated for hypoventilation or apnea. If respiratory depression is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled ventilation. Intravenous fluids and vasoactive agents may be required to manage hemodynamic instability.

DOSAGE AND ADMINISTRATION: The dosage of ALFENTA (alfentanil hydrochloride) should be individualized in each patient according to body weight, physical status, underlying pathological condition, use of other drugs, and type and duration of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of ALFENTA should be determined on the basis of lean body weight. The dose of ALFENTA should be reduced in elderly or debilitated patients (see PRECAUTIONS). Vital signs should be monitored routinely. Protect from light. Store at room temperature 15°-30° C (59°-86° F).

JANSSEN
PHARMACEUTICA
Piscataway, NJ 08855-3998

March 1987, April 1988
U.S. Patent No. 4,167,574
49-7619902-M

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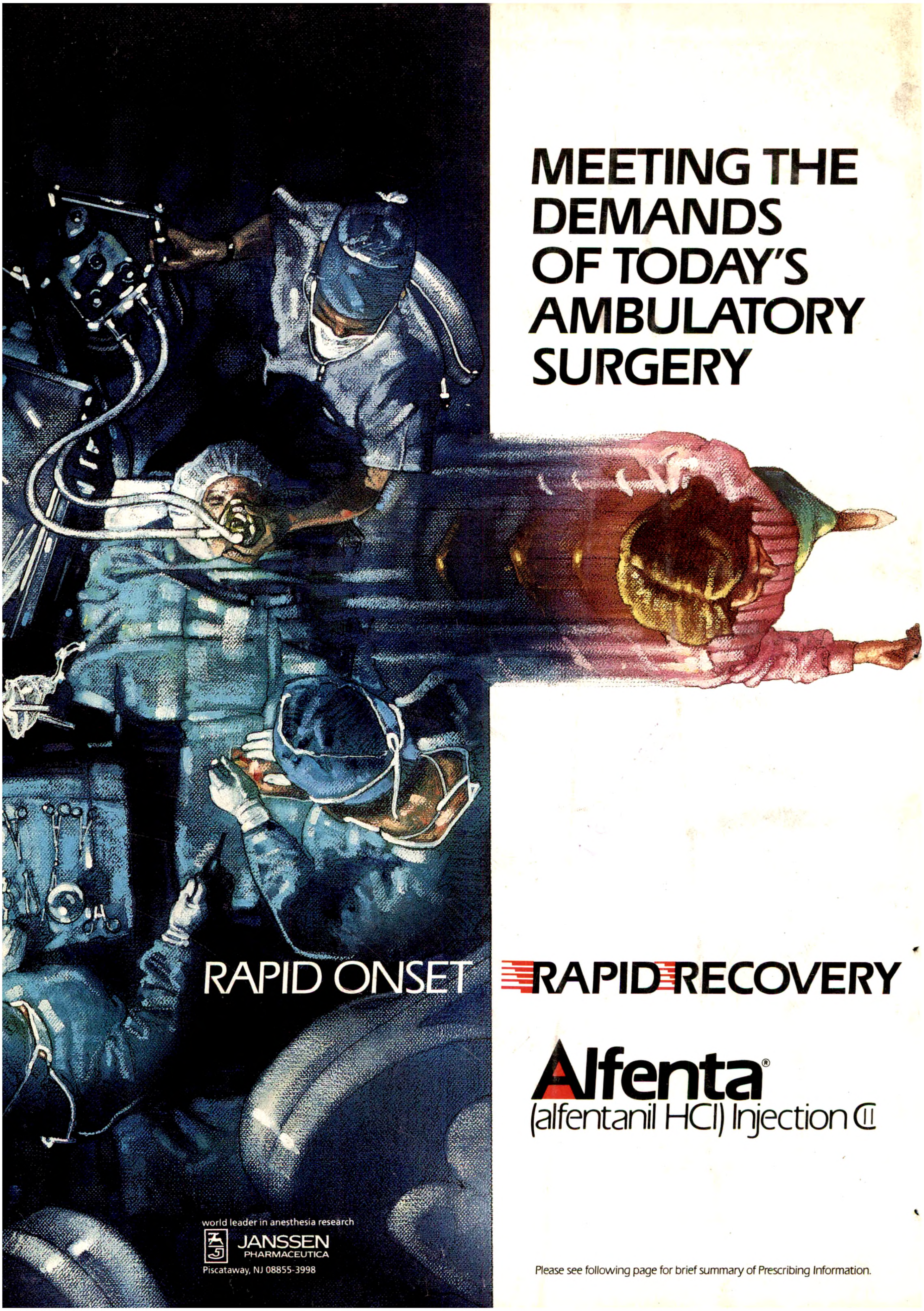

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0003-2999 Volume 75, Number 4, October 1992

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A LOGICAL CHOICE

CRUCIAL PARAMETERS IN SELECTING A NEUROMUSCULAR BLOCKING AGENT

	Norcuron® (vecuronium bromide) for injection	Atracurium besylate
HEMODYNAMICS	No significant variations in blood pressure, cardiac output, or systemic vascular resistance.[1]	Statistically significant variations in blood pressure, cardiac output, and systemic vascular resistance.[1] ($P<.05$)
HISTAMINE	Available clinical experience indicates that reactions commonly associated with histamine release are unlikely to occur.[1-4]	Precautions advised for patients in whom substantial histamine release would be hazardous (eg, clinically significant cardiovascular disease, asthma).[5]
RECOVERY		
To 25% of control	25-40 min[3]	35-45 min[5]
To 95% of control	45-65 min[3]	60-70 min[5]
DOSING FLEXIBILITY	The initial recommended dose is 0.08-0.1 mg/kg. Dose can be increased up to 0.28 mg/kg for long cases without significant histamine release or related cardiovascular side effects.[1,3,4]	Initial recommended dose is 0.4-0.5 mg/kg. A moderate histamine release and significant falls in blood pressure have been seen following a dose of 0.5 mg/kg ($P<.05$) and 0.6 mg/kg.[*2,5,6]
STORAGE & SHELF LIFE	2-year shelf life in lyophilized form at room temperature.[†] Can be reconstituted with various IV solutions including Lactated Ringers.[‡]	2-year shelf life under constant refrigeration.[†] Upon removal from refrigeration to room temperature storage, use within 14 days even if rerefrigerated.[5]

[*] Dose of atracurium above 0.5 mg/kg is not recommended.
[†] As originally supplied by the respective manufacturers.
[‡] Storage after reconstitution varies with solution. See package insert.

Norcuron®

(vecuronium bromide) for injection

A LOGICAL CHOICE FOR NEUROMUSCULAR BLOCKADE

See following page for brief summary of prescribing information.

Organon
ORGANON INC.
WEST ORANGE
NEW JERSEY 07052

Norcuron®
(vecuronium bromide) for injection

Before prescribing, please consult complete product information, a summary of which follows:

THIS DRUG SHOULD BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS.

CONTRAINDICATIONS: Norcuron® is contraindicated in patients known to have a hypersensitivity to it.

WARNINGS: NORCURON® SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION. TO REDUCE THE POSSIBILITY OF PROLONGED NEUROMUSCULAR BLOCKADE AND OTHER POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING LONG-TERM USE IN THE ICU, NORCURON® OR ANY OTHER NEUROMUSCULAR BLOCKING AGENT SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSES BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH ITS ACTIONS AND WHO ARE FAMILIAR WITH APPROPRIATE PERIPHERAL NERVE STIMULATOR MUSCLE MONITORING TECHNIQUES (see PRECAUTIONS). In patients who are known to have myasthenia gravis or the myasthenic (Eaton-Lambert) syndrome, small doses of Norcuron® may have profound effects. In such patients, a peripheral nerve stimulator and use of a small test dose may be of value in monitoring the response to administration of muscle relaxants.

PRECAUTIONS:

Renal Failure: Norcuron® is well tolerated without clinically significant prolongation of neuromuscular blocking effect in patients with renal failure who have been optimally prepared for surgery by dialysis. Under emergency conditions in anephric patients some prolongation of neuromuscular blockage may occur; therefore, if anephric patients cannot be prepared for non-elective surgery, a lower initial dose of Norcuron® should be considered.

Altered Circulation Time: Conditions associated with slower circulation time in cardiovascular disease, old age, edematous states resulting in increased volume of distribution may contribute to a delay in onset time, therefore dosage should not be increased.

Hepatic Disease: Limited experience in patients with cirrhosis or cholestasis has revealed prolonged recovery time in keeping with the role the liver plays in Norcuron® metabolism and excretion. Data currently available do not permit dosage recommendations in patients with impaired liver function.

Long-term Use in I.C.U.: In the intensive care unit, in rare cases, long-term use of neuromuscular blocking drugs to facilitate mechanical ventilation may be associated with prolonged paralysis and/or skeletal muscle weakness that may be first noted during attempts to wean such patients from the ventilator. Typically, such patients receive other drugs such as broad spectrum antibiotics, narcotics and/or steroids and may have electrolyte imbalance and diseases which lead to electrolyte imbalance, hypoxic episodes of varying duration, acid-base imbalance and extreme debilitation, any of which may enhance the actions of a neuromuscular blocking agent. Additionally, patients immobilized for extended periods frequently develop symptoms consistent with disuse muscle atrophy. The recovery picture may vary from regaining movement and strength in all muscles to initial recovery of movement of the facial and small muscles of the extremities then to the remaining muscles. In rare cases recovery may be over an extended period of time and may even, on occasion, involve rehabilitation. Therefore, when there is a need for long-term mechanical ventilation, the benefits-to-risk ratio of neuromuscular blockade must be considered. Continuous infusion or intermittent bolus dosing to support mechanical ventilation has not been studied sufficiently to support dosage recommendations.

IN THE INTENSIVE CARE UNIT, APPROPRIATE MONITORING, WITH THE USE OF A PERIPHERAL NERVE STIMULATOR TO ASSESS THE DEGREE OF NEUROMUSCULAR BLOCKADE, IS RECOMMENDED TO HELP PRECLUDE POSSIBLE PROLONGATION OF THE BLOCKADE. WHENEVER THE USE OF NORCURON® OR ANY NEUROMUSCULAR BLOCKING AGENT IS CONTEMPLATED IN THE ICU, IT IS RECOMMENDED THAT NEUROMUSCULAR TRANSMISSION BE MONITORED CONTINUOUSLY DURING ADMINISTRATION AND RECOVERY WITH THE HELP OF A NERVE STIMULATOR. ADDITIONAL DOSES OF NORCURON® OR ANY OTHER NEUROMUSCULAR BLOCKING AGENT SHOULD NOT BE GIVEN BEFORE THERE IS A DEFINITE RESPONSE TO T$_1$ OR TO THE FIRST TWITCH. IF NO RESPONSE IS ELICITED, INFUSION ADMINISTRATION SHOULD BE DISCONTINUED UNTIL A RESPONSE RETURNS.

Severe Obesity or Neuromuscular Disease: Patients with severe obesity or neuromuscular disease may pose airway and/or ventilatory problems requiring special care before, during and after the use of neuromuscular blocking agents such as Norcuron®.

Malignant Hyperthermia: Many drugs used in anesthetic practice are suspected of being capable of triggering a potentially fatal hypermetabolism of skeletal muscle known as malignant hyperthermia. There are insufficient data derived from screening in susceptible animals (swine) to establish whether or not Norcuron® is capable of triggering malignant hyperthermia.

C.N.S.: Norcuron® has no known effect on consciousness, the pain threshold or cerebration. Administration must be accompanied by adequate anesthesia or sedation.

Drug Interactions: Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron® (vecuronium bromide) for injection and its duration of action. If succinylcholine is used before Norcuron®, the administration of Norcuron® should be delayed until the succinylcholine effect shows signs of wearing off. With succinylcholine as the intubating agent, initial doses of 0.04-0.06 mg/kg of Norcuron® may be administered to produce complete neuromuscular block with clinical duration of action of 25-30 minutes. The use of Norcuron® before succinylcholine, in order to attenuate some of the side effects of succinylcholine, has not been sufficiently studied.

Other nondepolarizing neuromuscular blocking agents (pancuronium, d-tubocurarine, metocurine, and gallamine) act in the same fashion as does Norcuron®, therefore these drugs and Norcuron® may manifest an additive effect when used together. There are insufficient data to support concomitant use of Norcuron® and other competitive muscle relaxants in the same patient.

Inhalational Anesthetics: Use of volatile inhalational anesthetics such as enflurane, isoflurane, and halothane with Norcuron® will enhance neuromuscular blockade. Potentiation is most prominent with use of enflurane and isoflurane. With the above agents the initial dose of Norcuron® may be the same as with balanced anesthesia unless the inhalational anesthetic has been administered for a sufficient time at a sufficient dose to have reached clinical equilibrium.

Antibiotics: Parenteral/intraperitoneal administration of high doses of certain antibiotics may intensify or produce neuromuscular block on their own. The following antibiotics have been associated with various degrees of paralysis: aminoglycosides (such as neomycin, streptomycin, kanamycin, gentamicin, and dihydrostreptomycin); tetracyclines; bacitracin; polymyxin B; colistin; and sodium colistimethate. If these or other newly introduced antibiotics are used in conjunction with Norcuron®, unexpected prolongation of neuromuscular block should be considered a possibility.

Other: Experience concerning injection of quinidine during recovery from use of other muscle relaxants suggest that recurrent paralysis may occur. This possibility must also be considered for Norcuron®. Norcuron® induced neuromuscular blockade has been counteracted by alkalosis and enhanced by acidosis in experimental animals (cat). Electrolyte imbalance and diseases which lead to electrolyte imbalance, such as adrenal cortical insufficiency, have been shown to alter neuromuscular blockade. Depending on the nature of the imbalance, either enhancement or inhibition may be expected. Magnesium salts, administered for the management of toxemia of pregnancy, may enhance the neuromuscular blockade.

Drug/laboratory test interactions: None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential or impairment of fertility.

Pregnancy: Pregnancy Category C: Animal reproduction studies have not been conducted with Norcuron®. It is also not known whether Norcuron® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Norcuron® should be given to a pregnant woman only if clearly needed.

Pediatric Use: Infants under 1 year of age but older than 7 weeks, also tested under halothane anesthesia, are moderately more sensitive to Norcuron® on a mg/kg basis than adults and take about 1½ times as long to recover. Information presently available does not permit recommendations for usage in neonates.

ADVERSE REACTIONS: The most frequent adverse reaction to nondepolarizing blocking agents as a class consists of an extension of the drug's pharmacological action beyond the time period needed. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiration insufficiency or apnea.

Inadequate reversal of the neuromuscular blockade is possible with Norcuron® as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate. Little or no increase in intensity of blockade or duration of action of Norcuron® is noted from the use of thiobarbiturates, narcotic analgesics, nitrous oxide, or droperidol. See OVERDOSAGE for discussion of other drugs used in anesthetic practice which also cause respiratory depression.

Prolonged to profound extensions of paralysis and/or muscle weakness as well as muscle atrophy have been reported after long-term use to support mechanical ventilation in the intensive care unit (see PRECAUTIONS).

The administration of Norcuron® has been associated with rare instances of hypersensitivity reactions (bronchospasm, hypotension and/or tachycardia, sometimes associated with acute urticaria or erythema).

OVERDOSAGE: The possibility of iatrogenic overdosage can be minimized by carefully monitoring muscle twitch response to peripheral nerve stimulation.

Excessive doses of Norcuron® produce enhanced pharmacological effects. Residual neuromuscular blockage beyond the time period needed may occur with Norcuron® as with other neuromuscular blockers. This may be manifested by skeletal muscle weakness, decreased respiratory reserve, low tidal volume, or apnea. A peripheral nerve stimulator may be used to assess the degree of residual neuromuscular blockade from other causes of decreased respiratory reserve.

Respiratory depression may be due either wholly or in part to other drugs used during the conduct of general anesthesia such as narcotics, thiobarbiturates and other central nervous system depressants. Under such circumstances, the primary treatment is maintenance of a patent airway and manual or mechanical ventilation until complete recovery of normal respiration is assured. Regonol® (pyridostigmine bromide) injection, neostigmine, or edrophonium, in conjunction with atropine or glycopyrrolate will usually antagonize the skeletal muscle relaxant action of Norcuron®. Satisfactory reversal can be judged by adequacy of skeletal muscle tone and by adequacy of respiration. A peripheral nerve stimulator may also be used to monitor restoration of twitch height. Failure of prompt reversal (within 30 minutes) may occur in the presence of extreme debilitation, carcinomatosis, and with concomitant use of certain broad spectrum antibiotics, or anesthetic agents and other drugs which enhance neuromuscular blockade or cause respiratory depression of their own. Under such circumstances the management is the same as that of prolonged neuromuscular blockade. Ventilation must be supported by artificial means until the patient has resumed control

DOSAGE AND ADMINISTRATION: Before prescribing, please consult complete product information. Norcuron® (vec uronium bromide) for injection is for intravenous use only. This drug should be administered by or under the supervision experienced clinicians familiar with the use of neuromuscular blocking agents. Dosage must be individualized in each ca dosage information which follows is derived from studies based upon units of drug per unit of body weight and is intend serve as a guide only, especially regarding enhancement of neuromuscular blockade of Norcuron® by volatile anesthetic by prior use of succinylcholine (see PRECAUTIONS/Drug Interactions). Parenteral drug products should be inspected vi for particulate matter and discoloration prior to administration whenever solution and container permit.

To obtain maximum clinical benefits of Norcuron® and to minimize the possibility of overdosage, the monitoring of m twitch response to peripheral nerve stimulation is advised.

The recommended initial dose of Norcuron® is 0.08 to 0.10 mg/kg (1.4 to 1.75 times the ED$_{90}$) given as an intravenou injection. This dose can be expected to produce good or excellent non-emergency intubation conditions in 2.5 to 3 minu after injection. Under balanced anesthesia, clinically required neuromuscular blockade lasts approximately 25-30 minute recovery to 25% of control achieved approximately 25 to 40 minutes after injection and recovery to 95% of control achie approximately 45-65 minutes after injection. In the presence of potent inhalation anesthetics, the neuromuscular blockin of Norcuron® is enhanced. If Norcuron® is first administered more than 5 minutes after the start of inhalation agent or w steady state has been achieved, the initial Norcuron® dose may be reduced by approximately 15%, i.e., 0.060 to 0.085 n

Prior administration of succinylcholine may enhance the neuromuscular blocking effect and duration of action of Norc If intubation is performed using succinylcholine, a reduction of initial dose of Norcuron® to 0.04-0.06 mg/kg with inhala anesthesia and 0.05-0.06 mg/kg with balanced anesthesia may be required.

During prolonged surgical procedures, maintenance doses of 0.010 to 0.015 mg/kg of Norcuron® are recommended; a initial Norcuron® injection, the first maintenance dose will generally be required within 25 to 40 minutes. However, clinic ria should be used to determine the need for maintenance doses. Since Norcuron® lacks clinically important cumulative subsequent maintenance doses, if required, may be administered at relatively regular intervals for each patient, ranging a imately from 12 to 15 minutes under balanced anesthesia, slightly longer under inhalation agents. (If less frequent admin tion is desired, higher maintenance doses may be administered.)

Should there be reason for the selection of larger doses in individual patients, initial doses ranging from 0.15 mg/kg u 0.28 mg/kg have been administered during surgery under halothane anesthesia without ill effects to the cardiovascular s being noted as long as ventilation is properly maintained.

Use by Continuous Infusion: After an intubating dose of 80-100 µg/kg, a continuous infusion of 1 µg/kg/min can b ated approximately 20-40 min later. Infusion of Norcuron® should be initiated only after early evidence of spontaneous r from the bolus dose. Long-term intravenous infusion to support mechanical ventilation in the intensive care unit has not studied sufficiently to support dosage recommendations (see PRECAUTIONS).

The infusion of Norcuron® should be individualized for each patient. The rate of administration should be adjusted ac to the patient's twitch response as determined by peripheral nerve stimulation. An initial rate of 1 µg/kg/min is recomme with the rate of the infusion adjusted thereafter to maintain a 90% suppression of twitch response. Average infusion rates range from 0.8 to 1.2 µg/kg/min.

Inhalation anesthetics, particularly enflurane and isoflurane may enhance the neuromuscular blocking action of non-depolarizing muscle relaxants. In the presence of steady-state concentrations of enflurane or isoflurane, it may be necess reduce the rate of infusion 25-60 percent, 45-60 min after the intubating dose. Under halothane anesthesia it may not be essary to reduce the rate of infusion.

Spontaneous recovery and reversal of neuromuscular blockade following discontinuation of Norcuron® infusion may expected to proceed at rates comparable to that following a single bolus dose.

Infusion solutions of Norcuron® can be prepared by mixing Norcuron® with an appropriate infusion solution such as glucose in water, 0.9% NaCl, 5% glucose in saline, or Lactated Ringers. Unused portions of infusion solutions should b discarded.

Infusion rates of Norcuron® can be individualized for each patient using the following table:

Drug Delivery Rate (µg/kg/min)	Infusion Delivery Rate (mL/kg/min)	
	0.1 mg/mL*	0.2 mg/mL†
0.7	0.007	0.0035
0.8	0.008	0.0040
0.9	0.009	0.0045
1.0	0.010	0.0050
1.1	0.011	0.0055
1.2	0.012	0.0060
1.3	0.013	0.0065

*10 mg of Norcuron® in 100 mL solution †20 mg of Norcuron® in 100 mL solution

The following table is a guideline for mL/min delivery for a solution of 0.1 mg/mL (10 mg in 100 mL) with an infusion pu

NORCURON® INFUSION RATE – mL/MIN

Amount of Drug µg/kg/min	Patient Weight – kg						
	40	50	60	70	80	90	1
0.7	0.28	0.35	0.42	0.49	0.56	0.63	0.
0.8	0.32	0.40	0.48	0.56	0.64	0.72	0.
0.9	0.36	0.45	0.54	0.63	0.72	0.81	0.
1.0	0.40	0.50	0.60	0.70	0.80	0.90	1.
1.1	0.44	0.55	0.66	0.77	0.88	0.99	1.
1.2	0.48	0.60	0.72	0.84	0.96	1.08	1.
1.3	0.52	0.65	0.78	0.91	1.04	1.17	1.

NOTE: If a concentration of 0.2 mg/mL is used (20 mg in 100 mL), the rate should be decreased by one-half.

Dosage in Children: Older children (10 to 17 years of age) have approximately the same dosage requirements (mg/kg adults and may be managed the same way. Younger children (1 to 10 years of age) may require a slightly higher initial do may also require supplementation slightly more often than adults. Infants under one year of age but older than 7 weeks a moderately more sensitive to Norcuron® on a mg/kg basis than adults and take about 1½ times as long to recover. See a subsection of PRECAUTIONS titled Pediatric Use. Information presently available does not permit recommendation on us neonates (see PRECAUTIONS). There are insufficient data concerning continuous infusion of vecuronium in children, the no dosing recommendation can be made.

COMPATIBILITY: Norcuron® is compatible in solution with:

0.9% NaCl solution   Sterile water for injection   Lactated Ringers
5% glucose in water   5% glucose in saline

Use within 24 hours of mixing with the above solutions.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration ever solution and container permit.

HOW SUPPLIED:

10 mL vials (10 mg vecuronium bromide) and 10 mL prefilled syringes of diluent (bacteriostatic water for injection, USP). 22 g 1¼" needle.   Boxes of 10   NDC No. 0052-0441-60
10 mL vials (10 mg vecuronium bromide) and 10 mL vials of diluent (bacteriostatic water for injection, USP)
Boxes of 10   NDC No. 0052-0441-17
10 mL vials (10 mg vecuronium bromide) only; DILUENT NOT SUPPLIED.   Boxes of 10   NDC No. 0052-0441-1
20 mL vials (20 mg vecuronium bromide) only; DILUENT NOT SUPPLIED.   Boxes of 10   NDC No. 0052-0442-

STORAGE: 15°-30°C (59°-86°F). Protect from light.

AFTER RECONSTITUTION:

- When reconstituted with supplied bacteriostatic water for injection: CONTAINS BENZYL ALCHOHOL, WHICH IS NOT INTENDED FOR USE IN NEWBORNS. Use within 5 days. May be stored at room temperature or refrigerated.
- When reconstituted with sterile water for injection or other compatible I.V. solutions. Refrigerate vial. Use within 24 ho Single use only. Discard unused portion.

Caution: Federal law prohibits dispensing without prescription.

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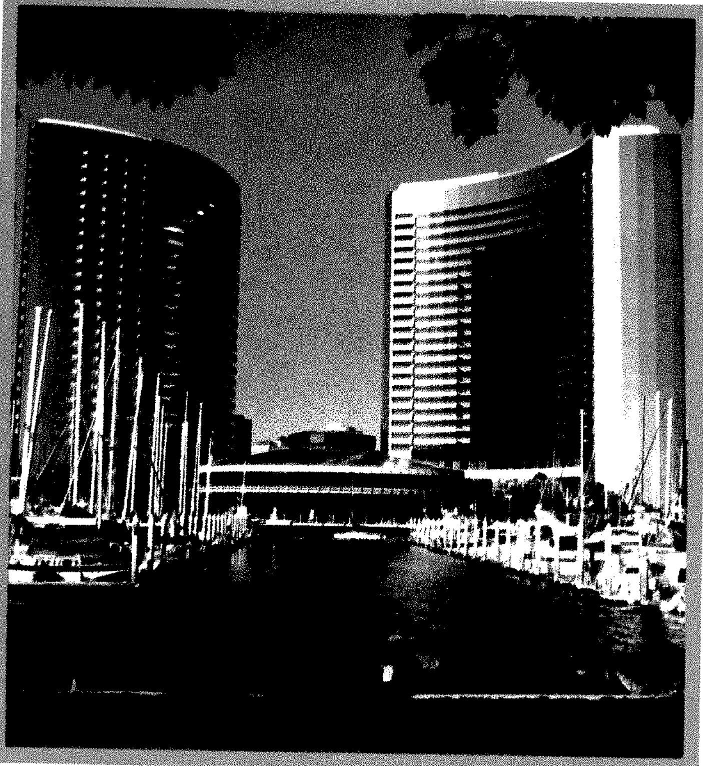

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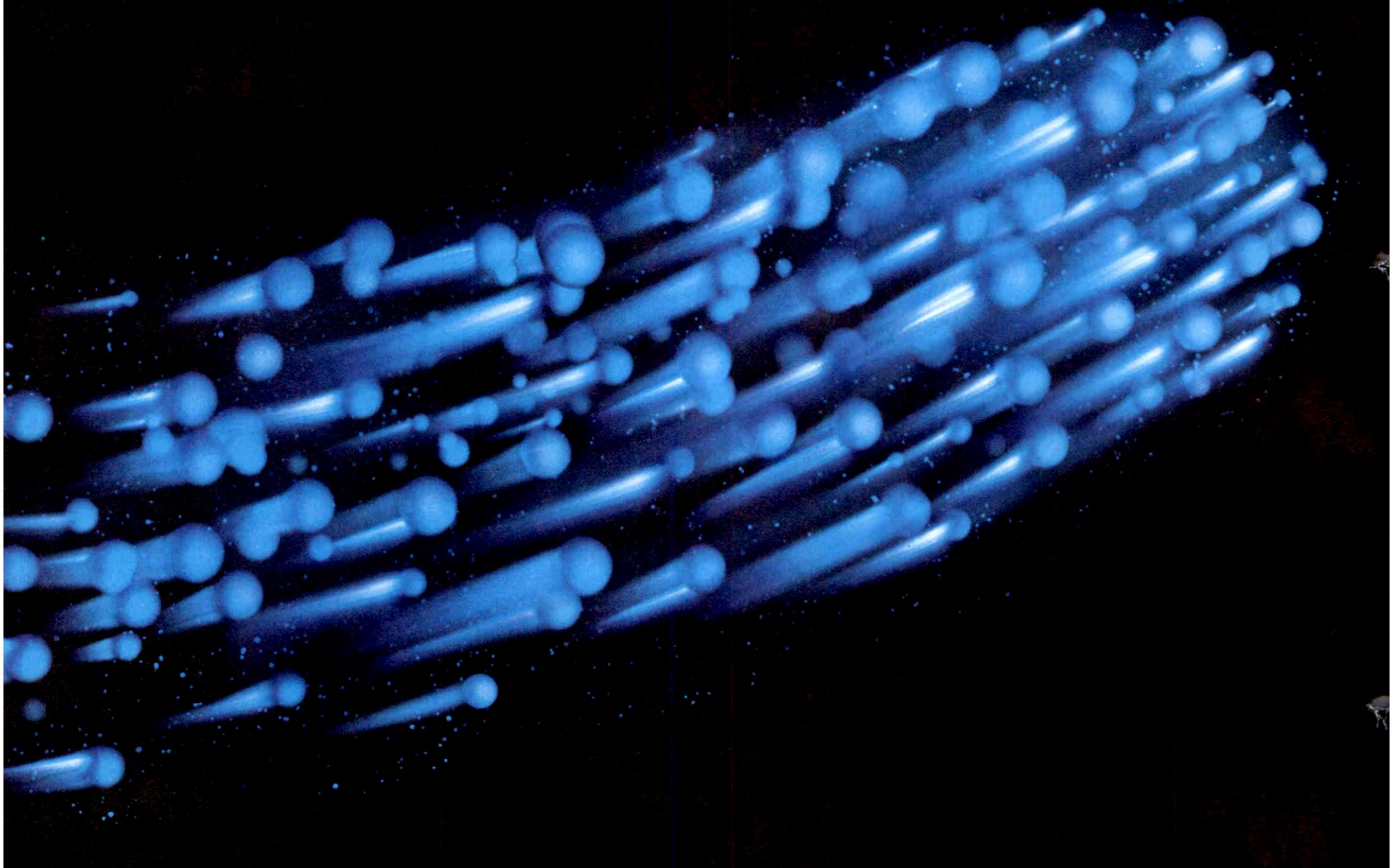

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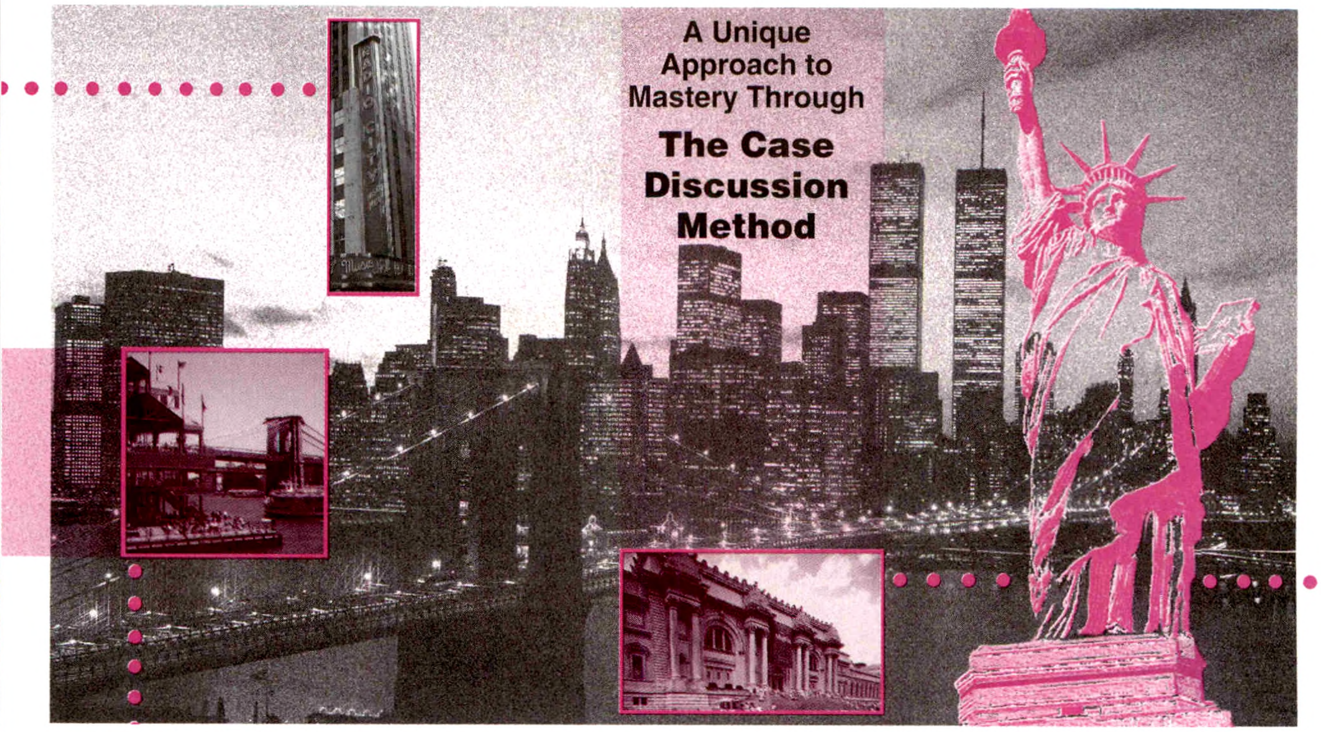

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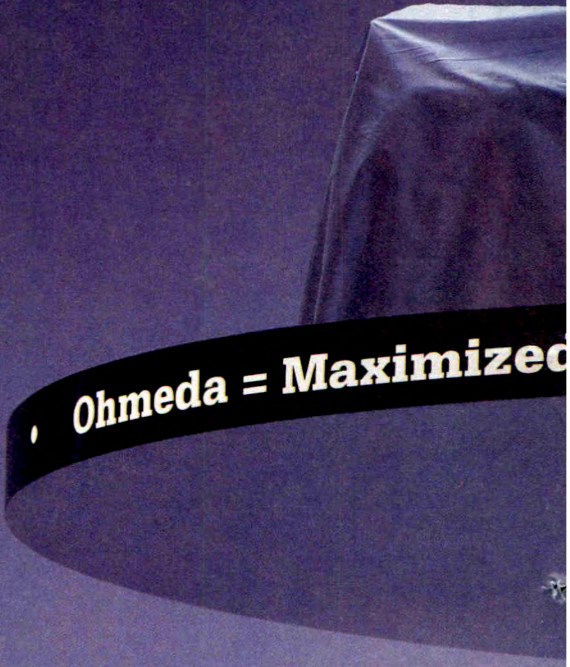

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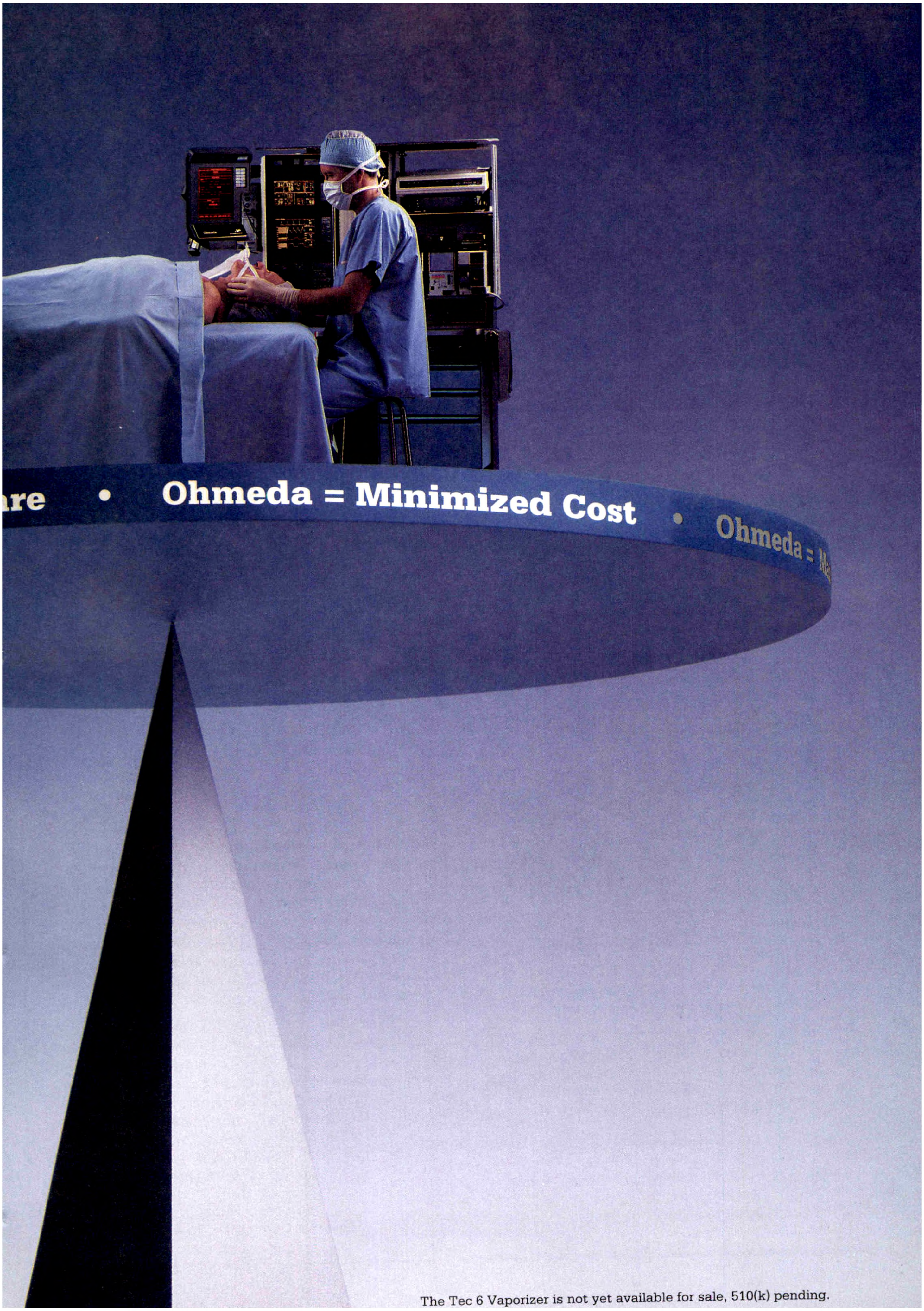
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Intraoperative Transesophageal Saline-Contrast Imaging of Flow-Patent Foramen Ovale

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Estimates of the prevalence of patent foramen ovale, defined by the ability to pass a probe through the foramen at autopsy (probe patency), have ranged from 25% to 35% (1,2). The reported prevalence of detectable flow across the foramen ovale (flow patency) under in vivo resting conditions has ranged from 5% to 10% (3–8). The sensitivity of patent foramen ovale flow patterns to changes in loading conditions is evidenced by the marked increase in flow-patency detection rates (18%–22%) that can occur when the hemodynamic milieu is manipulated by such provocative interventions as sudden release of positive intrathoracic pressure (Table 1). In this issue of *Anesthesia & Analgesia*, Jaffe et al. (8) report an association between application of mechanical ventilation and positive end-expiratory pressure in normal anesthetized patients and transesophageal saline-contrast imaging of right-to-left flow across previously unsuspected foramen ovale, further illustrating the dynamic nature of these interatrial communications.

The normal mean interatrial pressure gradient is from left to right. As mentioned, a standard technique for reversing this gradient consists of sudden release of positive airway pressure (3–8). The rationale for this method is as follows: during application of positive pressure, intrathoracic pressure increases, causing a decrease in right atrial filling and transmural pressure. With release of the positive pressure, blood rushes into the right atrium, causing right atrial pressure to transiently exceed left atrial pressure (3). Further, two studies pertaining to the effects of positive end-expiratory pressure on central hemodynamics tabulate measured right atrial pressure, together with such indirect indices of left atrial pressure as pulmonary capillary wedge pressure and pulmonary artery diastolic pressure (9,10). In neither of these reports is there evidence of reversal of the mean right atrial-left atrial pressure gradient with application of positive end-expiratory pressure. Accordingly, the data of Jaffe et al. (8) appear, superficially, to conflict with conventional wisdom; however, other issues must also be considered. First, a right-to-left pressure differential at any phase of the cardiac cycle would be expected to result in a positive diagnosis. Right and left atrial pressure changes are asynchronous, and a transient reversal of gradient often occurs in early systole (11). Accordingly, analysis of mean pressure differentials may be misleading. Second, as emphasized by Jardin et al. (9), considerable individual variation exists in the hemodynamic response to positive end-expiratory pressure. Third, the foramen ovale is a flap valve, and altered cardiac geometry, with distortion of septal configuration, has been implicated in the genesis of flow patency of the foramen ovale after pneumonectomy (12). Finally, specific flow patterns within the right atrium may also influence flow across the septum. Swan et al. (13) have demonstrated that inferior vena cava venous return is normally preferentially directed toward the foramen ovale. In contrast, Langholz et al. (14) have reported a case where juxtaposition of a right atrial mass and the superior vena cava caused streaming of venous return toward a flow-patent foramen ovale that was ultimately associated with a fatal paradoxical embolus. As Jaffe et al. (8) state, a complete understanding of the factors affecting interatrial pressure gradients in the absence of preexisting pulmonary hypertension requires additional study.

The clinical implications of flow patency of the foramen ovale in patients undergoing surgery are well recognized. Flow patency has been characterized both as a risk factor for paradoxical embolization and as a possible cause of unexplained hypoxemia (12,15–18). Guggiari et al. (5) considered demonstration of a right-to-left shunt as representing an absolute contraindication to craniectomy in the sitting position. Black et al. (6) and Cucchiara et al. (15) also suggested that an evaluation of flow patency is an important part of the assessment of such patients, with intraoperative transesophageal echocardiographic definition

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Table 1. Prevalence of Flow-Patent Foramen Ovale

Reference	No. of Pts	"Window"	Basal conditions (%)	Provocation (% release of positive pressure)
Lynch et al. (3) (1984)	76	TTE	5	18
Lechat et al. (4) (1988)	100	TTE	5	10
	60		18[a]	24[a]
Guggiari et al. (5) (1988)	189	TTE	8	10
Black et al. (6) (1990)	101	TTE	6	Unchanged
	51	TEE	8	—
Konstadt et al. (7) (1991)[b]	50	TEE	10	22
Jaffe et al. (8) (1992)	30	TEE	10[c]	Unchanged

Pts, patients; TTE, transthoracic echocardiography; TEE, transesophageal echocardiography.

[a] Status postcerebrovascular accident.

[b] Combined saline-contrast, color flow, and pulsed Doppler study.

[c] Positive end-expiratory pressure.

Table 2. False-Negative Transesophageal Echocardiography Saline-Contrast Studies

Reference	Technique	Result
Cucchiara et al. (15) (1984)	TEE 4-chamber view	False-negative defined by subsequent TEE diagnosis during actual VAE
Cucchiara et al. (16) (1985)	TEE 4- and 5-chamber views	False-negative defined by subsequent (3 h) TEE positive saline-contrast study, TEE during actual VAE, and postoperative transthoracic saline-contrast study, respectively
Cucchiara et al. (17) (1989)	Transthoracic and TEE 4-chamber view	False-negative defined by subsequent TEE diagnosis during actual VAE
Black et al. (6) (1990)	TEE	False-negative defined by preoperative positive transthoracic saline-contrast study
Konstadt et al. (7) (1991)	TEE biatrial basal short-axis view	False-negative defined by positive TEE color flow Doppler and pulsed Doppler study

TEE, transesophageal echocardiography; VAE, venous air embolism.

allowing the clinician the choice of altering patient position before the operation has begun. Black et al. (19) have also recommended the avoidance of positive end-expiratory pressure in the sitting position. Their conclusions were based on data derived from an animal model with a surgically created atrial septal defect. The report by Jaffe et al. (8) consolidates this recommendation. Because of the prevalence of flow patency, the authors further suggest that any patient maintained on mechanical ventilation, particularly those requiring positive end-expiratory pressure, may be at particular risk for paradoxical embolization after inadvertent introduction of air at a wound or venous access site. Konstadt et al. (7) have addressed the circumstances of diagnosis of flow patency during an ongoing closed cardiac procedure, such as coronary revascularization. These authors have concluded that the additional surgical risk involved in closure of the defect may be justified in patients with a history of unexplained transient ischemic attacks for which paradoxical emboli may be the cause. Any such intraoperative decision must include an overall cardiac evaluation lest the foramen represent a functional left atrial decompression vent mitigating against pulmonary edema, as occurred in our institution in a case with mitral regurgitation, and a definitive decision may be deferred pending ventriculography. Finally, Vacek et al. (12) and Dewan et al. (18) have reported two instances where severe postoperative hypoxemia was definitively due to shunting through previously unsuspected foramen ovale.

The study of Jaffe et al. (8) utilized saline-contrast definition of a right-to-left shunt to delineate flow patency of the foramen ovale. This technique has the disadvantage that no right-to-left shunting may be apparent under basal conditions because the mean left atrial pressure normally exceeds that of the right atrium. A left-to-right shunt can be defined by saline-contrast imaging, the so-called negative saline-contrast technique (20). In this method, the shunt is inferred by visualization of an area without contrast within a contrast-containing right atrium. The "negative" area is due to displacement of contrast-containing blood by non-contrast-containing left atrial blood (20). Unfortunately, this finding can be subtle, particularly so under conditions of tachycardia (21). On the other hand, the appearance of contrast in the left atrium is unequivocal, and no further steps are required to establish the diagnosis (22). Black et al. (6) have stated that the sensitivity of transesophageal echocardiography is such that the likelihood of clinically significant paradoxical embolism not being imaged is remote with this form of monitoring. However, it must be stressed that saline-contrast diagnostic studies of atrial septum integrity may often be associated with false-negative results, even when performed in association with a provocative maneuver (Table 2). Accordingly, although a positive test is definitive, a negative diagnostic study does not preclude subsequent flow patency.

It is generally accepted that echocardiography is an operator-dependent technique. Accurate diagnosis is

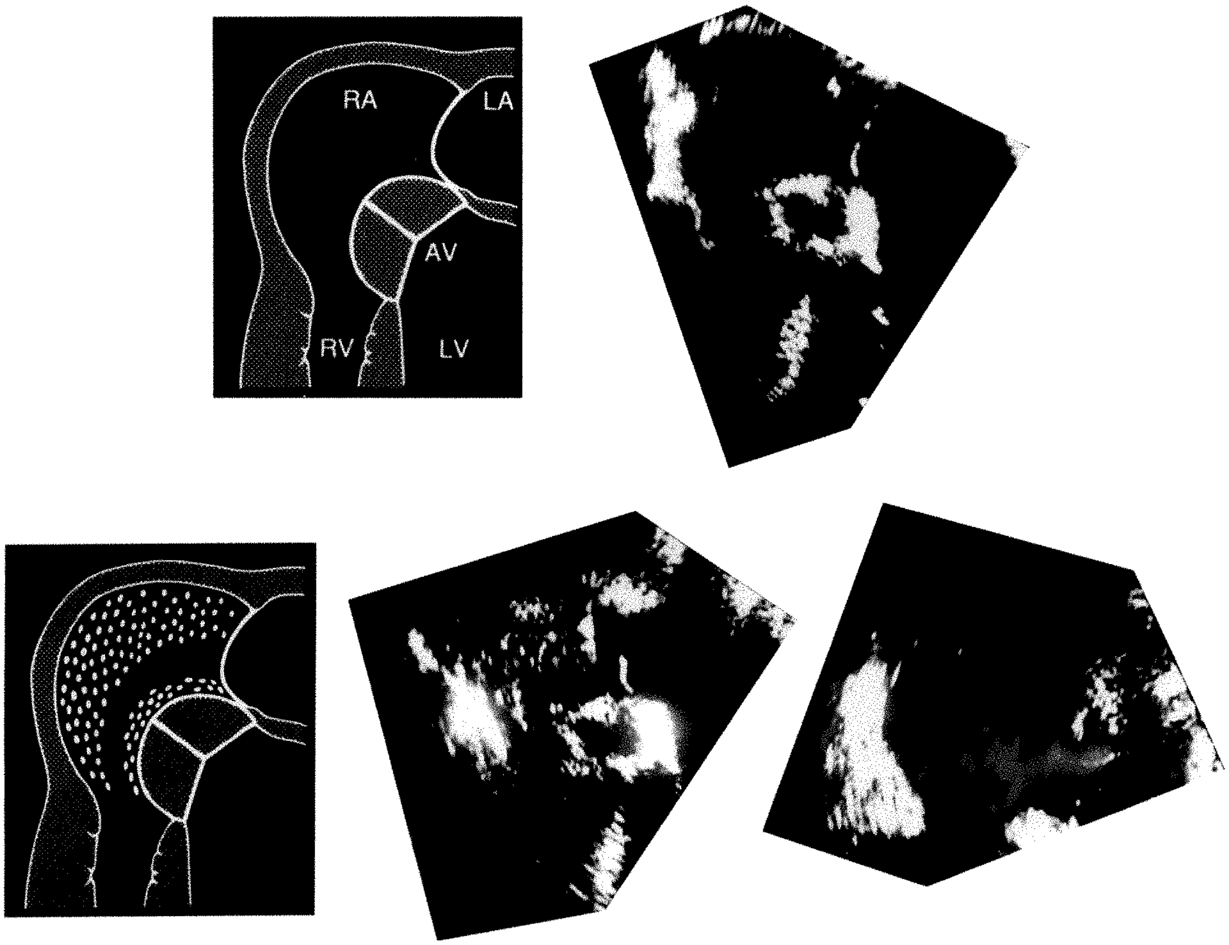

Figure 1. Patent foramen ovale with negative saline-contrast diagnosis of left-to-right shunt. *Upper panels,* Representation of left-to-right interatrial pressure gradient evidenced by bowing of the septum to the right. *Lower left and middle panels,* Left atrial blood containing no contrast has displaced the contrast-containing blood in the right atrium. *Lower right panel,* The area of negative saline-contrast in the lower left and middle panels corresponds to the color-flow-Doppler-defined left-to-right flow. RA, right atrium; LA, left atrium; RV, right ventricle; LV, left ventricle; AV, aortic valve.

inexorably tied to performance of a technically adequate examination (23). Performance of a complete saline-contrast evaluation of the foramen ovale involves two-dimensional echocardiographic analysis of the atria in conjunction with intravenous administration of hand-agitated saline, timed to achieve right atrial opacification with the agitated saline synchronous with sudden release of positive airway pressure. Although such general factors relating to acquisition of quality images as optimization of coarse and time-gain settings are pertinent, there are technical considerations specific to (a) imaging of the atria, (b) production of adequate opacification, and (c) definition of the appropriate level of airway pressure to be used in any provocative maneuver. Seward et al. (24) have noted that the atrial septum is evident in multiple short- and long-axis transesophageal transverse plane tomographic projections. These authors have defined a comprehensive transverse plane assessment as encompassing both a biatrial cephalad basal short-axis scan at aortic valve level and a more caudad long-axis four-chamber view (24). Biplane imaging provides the capacity to examine the atria and septum in a longitudinal plane. Longitudinal plane views image extreme anterior and posterior structures and provide access to the atrial septum along its greater length (25,26). This can be particularly useful in the setting of aortic root dilation, where the septum can appear especially shortened on short-axis imaging (26). Clearly, a thorough examination with technically acceptable images demands a degree of expertise.

An appreciation of the technical limitations of saline-contrast imaging demands an understanding

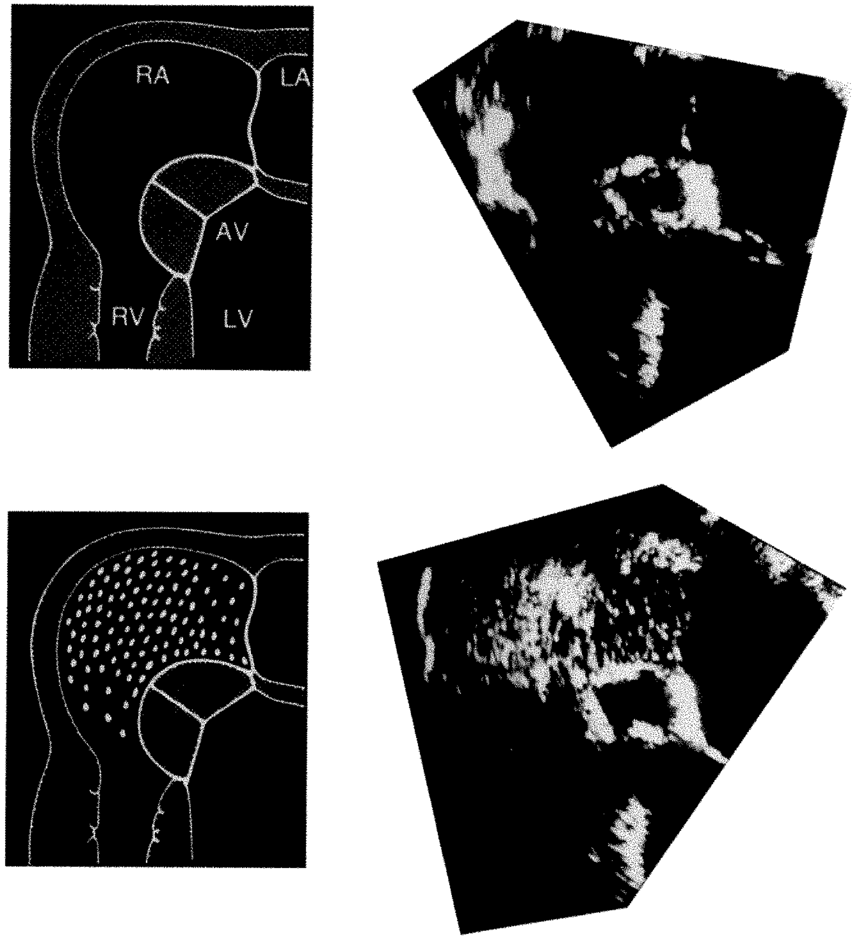

Figure 2. Patent foramen ovale with conditions of zero flow. *Upper panels,* The interatrial septum can be seen to have assumed a midline position, reflecting the absence of a pressure gradient between the atria. *Lower panels,* Saline-contrast imaging does not depict the septal defect, emphasizing the importance of utilizing an endpoint to avoid false-negative diagnoses.

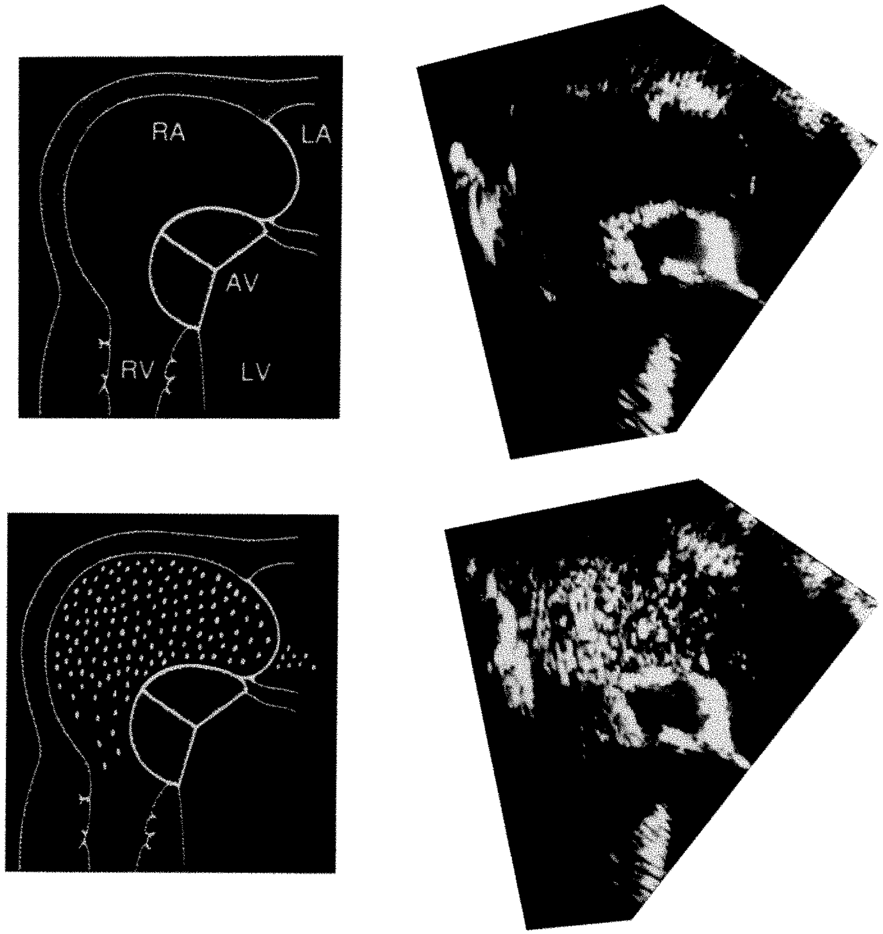

Figure 3. Patent foramen ovale with saline-contrast definition of a right-to-left shunt. *Upper panels,* Representation of a right-to-left interatrial pressure gradient evidenced by bowing of the septum to the left. *Lower panels,* Saline-contrast can be seen to traverse the septum into the left atrium.

of the mechanism whereby injected saline can function as an ultrasound-opaque medium and thus opacify intracardiac structures. Rapid injection of any gas-containing solution through a small-bore orifice causes microbubbles to form within the solution. This microbubble formation is a consequence of the pressure decrease at the orifice (Bernouilli principle) that allows the dissolved gases to escape from solution (21). These microbubbles within the saline provide the source of contrast. Saline-contrast echocardiography represents an echocardiography imaging method whereby microbubbles are intentionally produced by preinjection agitation of saline. With peripheral venous (rather than central) injection of hand-agitated saline, the microbubbles within the solution may have redissolved too rapidly to be of diagnostic value. In addition, the transit time within the atrium in patients with normal hemodynamics may be so brief as to make it difficult to synchronize adequate chamber opacification with the various manipulations of intrathoracic pressure. Parenthetically, patients with depressed right ventricular function or tricuspid incompetence are technically less challenging, owing to decreased transit time in the former situation and "reconcentration" of the contrast by the regurgitation in the latter instance (27,28). Finally, the effects of the various manipulations of airway pressure may not be sufficient to induce a right-to-left gradient under the conditions of the saline-contrast study, owing to such factors as adequate right ventricular reserve or a disproportionate baseline left atrial pressure. With changing clinical circumstances, the differential between right and left heart pressures may then allow paradoxical embolization or indeed cause clinically meaningful right-to-left shunt-associated hypoxemia. As emphasized by Konstadt et al. (7), confidence in negative results requires documentation that the release of positive airway pressure has indeed created a pressure-gradient reversal. In one patient in their series, there was no shunting during apnea or after release of 20 cm H_2O positive airway pressure. It was noted that the right atrial pressure did not exceed the pulmonary capillary wedge pressure at any time during the cardiac cycle. Contrast injection was repeated after release of 30 cm H_2O positive airway pressure, a step that resulted in transient elevation of right atrial pressure over pulmonary capillary wedge pressure and right-to-left shunting of contrast. These authors have recommended that the anatomic configuration of the atrial septum be used as an endpoint for assessing the efficacy of interventions used to induce a right-to-left gradient. The compliance of the septum is such that even minor changes in pressure differential that normally occur during a cardiac cycle are reflected by detectable changes in spatial orientation (29). Accordingly, it would seem prudent to visually confirm leftward displacement of the septum before cases are accepted to have a negative saline-contrast study result. These technical aspects are illustrated in Figures 1–3, representing an incidental patent foramen ovale in a 68-yr-old patient undergoing coronary artery bypass graft surgery, whereby a left-to-right shunt, zero flow, and a right-to-left shunt were evoked by manipulation of airway pressure. Accordingly, although it is clear that saline-contrast evaluation of the integrity of the atrial septum should be part of minimal reporting requirements during intraoperative transesophageal echocardiographic monitoring, complementing color flow and pulsed Doppler examinations, it is essential that imaging limitations be recognized.

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Venovenous Bypass During Liver Transplantation

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In this issue of *Anesthesia and Analgesia*, Veroli and colleagues (1) explore an important aspect of the intraoperative management of liver transplantation: the use of venovenous bypass hemodynamic support during the anhepatic period. Liver transplantation is an effective therapy for a variety of acute and chronic liver diseases that result in hepatic failure. Much of the improvement in survival statistics can be attributed to advances in immunosuppressive management, particularly the introduction of cyclosporine and the earlier recognition of rejection episodes. However, despite nearly 30 yr of clinical experience in human liver transplantation, the intraoperative management of this procedure remains challenging for anesthesiologists and surgeons. The magnitude of the surgical procedure (i.e., total hepatectomy, porta hepatis dissection, four major vascular anastomoses, and biliary reconstruction) in patients with severe liver disease (i.e., portal hypertension, coagulopathy, and thrombocytopenia) accounts for much of the difficulty encountered with this procedure. In addition, the critical part of the operation, the anhepatic period, requires the vascular exclusion of the liver to permit anastomosis and subsequent reperfusion of the hepatic allograft. This time period (30–90 min) is marked by significant changes in cardiovascular indices: decreased filling pressure, decreased cardiac output, increased infrahepatic caval pressure, decreased renal perfusion pressure, and moderately decreased systemic arterial pressure. To attenuate some of these hemodynamic responses, venovenous bypass was introduced to facilitate venous return of blood from the lower extremities and portal system to the upper body (2). Additional perioperative benefits attributed to venovenous bypass include decreased bleeding and transfusion requirement, improved postoperative renal function, decompression of the intestinal vascular bed, and earlier return of intestinal function; a better environment in which to train transplant surgeons is also an important benefit (3). Because the potential benefits of venovenous bypass appear to be significant, many transplant centers have adopted routine use of bypass during liver transplantation. However, there is an increasing number of case reports and clinical experience that associate significant complications with the use of the bypass technique: air embolism, thromboembolism, trauma to the brachial plexus and cannulated vessels, increased surgical time, and increases in incidence and severity of hypothermia (4,5).

Ideally, the overall benefits of venovenous bypass should be assessed by measuring specific outcome variables in randomized clinical trials. Hemodynamic instability, although worrisome to clinicians, is not a precise outcome; renal failure, blood product utilization, early graft function, and patient morbidity and mortality are among the important outcome variables to assess. Presently, no outcome studies are available to evaluate the benefits of venovenous bypass. Transplant centers and physicians must evaluate their use of this technique by balancing the benefits of this technique against the risks. Currently, the use of venovenous bypass at different centers ranges from never to universal application in adult patients. With the increasing frequency of liver transplantation, it is essential that we evaluate closely the potential benefits and adversities associated with venovenous bypass.

Veroli and colleagues (1) examine one of the purported benefits of venovenous bypass: preservation of postoperative renal function. Perioperative renal function is a complicated issue in patients undergoing liver transplantation. Preoperatively, patients with end-stage liver disease may manifest renal dysfunction. The etiology of preoperative renal dysfunction includes the usual differential diagnoses; in addition, the hepatorenal syndrome may be evident in 10%–15% of patients presenting for liver transplantation. Intraoperatively, the kidney is subjected to a variety of insults that may impact on postoperative function: dramatic changes in hemodynamics, alterations in renal perfusion pressure, and cyclosporine administration. Postoperatively, the kidney is vulnerable to additional insults, particularly those caused by the use of cyclosporine and other nephrotoxic agents. Several studies have documented a reduction of

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approximately 30%–40% in glomerular filtration rate after liver transplantation in patients with previously normal renal function. Postoperative renal failure is particularly deleterious in liver transplant patients and has been associated with an extremely high perioperative mortality (6). Previous investigators have explored other avenues of renal protection, including intraoperative dopamine (7) and verapamil (8), but have been unable to attenuate postoperative renal dysfunction.

Venovenous bypass may modulate postoperative renal dysfunction. As indicated earlier, it is known to ameliorate some of the acute hemodynamic changes during the anhepatic period and can usually preserve normal renal perfusion pressure during this stage (8–10). However, because the kidneys are subject to multiple insults in the perioperative period of hepatic transplantation, simply maintaining normal systemic and renal hemodynamics may not be sufficient to prevent postoperative renal dysfunction.

Interpreting the results of the Veroli et al. (1) study requires particular attention. Their study design was limited by the patterns of care within the institution: they believed it necessary to provide venovenous bypass support to patients who developed marked hemodynamic instability (a decrease in mean arterial pressure >30% or a decrease in cardiac index >50%, or both) in response to a trial period of hepatic vascular occlusion. They also believed that the possible risks of bypass prevented random assignment of the technique to patients who did not require it for cardiovascular support. Nonetheless, their study provides results important for anesthesiologists and surgeons involved in these procedures. Specifically, use of the trial period of hepatic vascular occlusion permitted identification of two distinct populations of patients undergoing liver transplantation. Patterns of collateral flow or degrees of reflex responsiveness to hepatic vascular exclusion, or both, are likely to have been different in patients who tolerated the trial within the limits assigned and in those unable to maintain blood pressure or cardiac index. Readers must recognize that the limits selected by Veroli et al. (1) were arbitrary; there have been no prospective studies performed to determine the deleterious effects, if any, of the changes in arterial pressure or cardiac index.

Nevertheless patients were assigned to two separate groups, and venovenous bypass support was utilized in the patients with marked hemodynamic changes in response to the test clamp. Veroli et al. (1) were unable to discern a significant difference in postoperative renal function (as measured by serum creatinine on the third postoperative day) despite significant differences in the renal hemodynamics and urine output during the anhepatic phase. These findings allow us to conclude that patients with normal renal function preoperatively, and who tolerate the trial period of hepatic vascular exclusion, do not require the use of venovenous bypass to prevent postoperative renal failure. In addition, patients managed without bypass did not require increased intraoperative blood products support compared with patients in whom bypass was used.

It is important to realize the additional, and perhaps most significant, limitations of this study. The use of bypass in the patients who did not appear to "require" bypass for hemodynamic support was not tested. It is possible that if these patients had received bypass support, their renal function or blood loss, or both, might have been better. Similarly, the value to outcome in maintaining arterial blood pressure and cardiac index in patients who were supported with bypass was not fully assessed. The data presented by Veroli et al. (1) are insufficient to determine whether the patients who demonstrated moderate hemodynamic instability during the trial period of hepatic vascular exclusion benefited from the use of venovenous bypass. Readers of the Veroli et al. (1) study will be unable to conclude whether the use of bypass in these patients was necessary to preserve renal function or whether the only impact was on the measured hemodynamic variables that Veroli et al. (1) report.

In an ideal study, a random assignment to venovenous bypass support would provide answers to many questions with regard to the purported benefits of this technique. As mentioned in the report by Veroli et al. (1), such a study would require a very large number of patients to avoid a type II error. Specifically, given the incidence of postoperative renal dysfunction and an anticipated benefit from venovenous bypass of 50% (i.e., that the incidence of postoperative renal dysfunction would be reduced from 20% to 10%), an adequate study would require approximately 700 patients. Studies lacking adequate sample size are at risk for declaring no benefit from venovenous bypass when, in fact, a benefit did exist. Similarly, although Veroli et al. (1) found no demonstrable evidence of a difference in renal function in patients managed with or without venovenous bypass, they were unable to claim that venovenous bypass is without benefit.

In summary, this study, despite its limitations, suggests an important change for the management of hepatic transplantation. In a single institution, the selective utilization of venovenous bypass support based on a trial period of hepatic vascular exclusion did not have an adverse impact on postoperative renal function, surgical duration, or transfusion requirement. Additional centers should consider future studies designed to identify which patients, if any, need or will benefit from venovenous bypass support. Until such studies are performed, Veroli et al. (1) have provided good evidence that routine and systematic use of venovenous bypass is not an absolute requirement.

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Aspects of Mechanical Ventilation Affecting Interatrial Shunt Flow During General Anesthesia

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Intraoperative transesophageal echocardiography was used to study the incidence of flow-patent foramen ovale in 33 normal, healthy patients (ASA physical status I) undergoing general anesthesia in the supine position for nonthoracic surgical procedures. Echocardiographic contrast was injected intravenously during mechanical ventilation in the presence of 0, 5, 10, 15, or 19 cm H_2O positive end-expiratory pressure (PEEP). A final test was performed during the release of 19 cm H_2O PEEP. The presence of a flow-patent foramen ovale was detected when the injected echo targets were observed crossing the interatrial septum from right to left. Most interesting, 3 of 33 patients developed a right-to-left shunt that was first detected with the steady application of 10 (1 patient) or 15 cm H_2O PEEP (2 patients). In all three cases, the shunt flow was accentuated on the release of PEEP; however, no additional cases were detected using this respiratory maneuver. These cases represent the first demonstration of right-to-left interatrial shunting evoked as the result of the sustained application of PEEP. This study also revealed a lower than expected incidence of flow-patent foramen ovale (9%) when measured during general anesthesia and positive pressure ventilation with or without PEEP.

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The incidence of venous air embolism (VAE) during general or regional anesthesia in the supine position has been reported for a variety of surgical procedures, including craniectomy (41%–66%) (1,2), cesarean section (50%) (3), and hip replacement surgery (30%) (4). Although the likelihood of VAE during these procedures is substantial, clinical manifestations of VAE are often undetectable, because the volume of embolized air is small and the filtering capacity of the lungs is rarely exceeded.

Paradoxical VAE can occur when air crosses from the systemic venous to the systemic arterial circulation without passing through the pulmonary capillary filter. Most commonly, crossover is believed to occur through a patent foramen ovale (PFO). On the basis of an extensive autopsy series (5), the incidence of probe-PFO in an adult population is 27% (range 19%–36%), with the highest incidence found during the first three decades of life. Thus, a significant percentage of patients, as high as 24% (i.e., 36% of the 66% incidence of VAE seen in supine craniectomies), undergoing selected surgical procedures in the supine position are at risk for paradoxical VAE, with its consequent risk of cerebral or myocardial embolization and infarction (6,7).

The preoperative identification of patients at risk for paradoxical VAE has been the subject of several recent echocardiographic studies that reported prevalence rates of 6%–18% (7–10). However, the sensitivity and specificity of precordial echocardiography in preoperative screening may not be adequate to identify every patient at risk for paradoxical VAE (11,12). For example, several studies utilizing screening tests with precordial Doppler failed to identify patients in whom paradoxical embolism did occur (9,13,14). Although the relative merits of the various preoperative screening methods can be debated, it is clear that high priority should be given to the identification of those factors that can affect interatrial shunt flow in the anesthetized patient. In this way, it may be possible to enhance patient safety while minimizing the need for preoperative screening tests.

The use of mechanical ventilation with or without positive end-expiratory pressure (PEEP) is common during general anesthesia and in the intensive care unit setting. The release of high levels of PEEP (analogous to the release of a Valsalva maneuver) can evoke shunt flow through a PFO. Unknown, how-

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ever, is the extent to which cyclic intrathoracic and airway pressure changes produced during mechanical ventilation may repeatedly mimic the pressure changes produced on the release of PEEP. Thus, it is possible that mechanical ventilation may produce recurring opportunities for right-to-left interatrial shunt flow with the attendant risk for paradoxical embolization.

The goals of the present study were (a) to examine the effects of mechanical ventilation and sustained PEEP on the occurrence of right-to-left interatrial shunt flow during general anesthesia in a healthy patient population undergoing general surgery, and (b) to describe the incidence of PFO using a traditional respiratory maneuver (PEEP release) and transesophageal echocardiography (TEE) in this same population.

Methods

This study was approved by the Stanford University Medical Committee for the Protection of Human Subjects in Research, and written consent was obtained from all subjects. Thirty-three patients (13 male, 20 female; mean age 32 yr; range 21–55 yr; ASA physical status I) scheduled for nonthoracic surgery in the supine position were included in this study. Excluded from this study were patients with any history of cardiovascular, pulmonary, or esophageal disease. The conduct of anesthesia was left to the judgment of each patient's attending anesthesiologist, who played no part in the study. Typically, anesthesia was induced with thiopental (3–5 mg/kg IV) and maintained with a combination of isoflurane in an oxygen/nitrous oxide mixture. Tracheal intubation was accomplished after administration of a muscle relaxant, and muscle relaxation was maintained with a nondepolarizing agent. Routine monitoring included electrocardiography, noninvasive blood pressure monitoring, pulse oximetry, capnography, and mass spectrometry.

All ultrasound recordings were obtained using a Hewlett-Packard ultrasonograph (model Sonus 500, Andover, Mass.) with a 5-MHz single-plane transducer mounted at the tip of a 14-mm flexible adult gastroscope (model 21362A, Hewlett Packard echoscope). All studies were performed within the first hour of general anesthesia, with the patient in a supine position. The TEE probe was introduced into the esophagus with the transducer facing anteriorly. Tomographic planes were obtained in the usual fashion by translating and rotating the echoscope within the esophagus while observing the ultrasonic image for reference (15). Modified four-chamber (biatrial) views were used to allow optimal visualization of the interatrial septum and left and right atria. All of the echocardiographic examinations were performed by experienced echocardiographers.

Each subject was tested during the sustained application (>30 s) of 0, 5, 10, 15, and 19 cm H_2O PEEP during mechanical ventilation using a tidal volume of 10–15 mL/kg at a frequency of 6–10 breaths/min. The final test was performed during the release of 19 cm H_2O PEEP. Echo contrast was produced by the vigorous agitation of 10 mL of saline with a small volume of air using a two-syringe technique (creating microbubble echo targets). After excluding macroscopic bubbles, the saline was rapidly injected into a peripheral vein of an upper extremity. A contrast injection was deemed adequate only if the right atrium became completely opacified by echo targets. This often required more than one injection. A test was considered positive if injected echo targets were observed to cross the interatrial septum from right-to-left. All TEE data were recorded on videotape and subsequently analyzed by an independent echocardiographer.

Results

Right-to-left interatrial shunt flow was observed in 3 (9%) of 33 healthy patients during mechanical ventilation and general anesthesia for noncardiac surgery (Figure 1). In one of these patients, as previously presented in a case report (16), episodic interatrial shunt flow was observed coincident with early inspiration at 0, 5, and 10 cm H_2O PEEP, becoming independent of respiratory phase at higher levels of PEEP. Shunt flow in the other two patients was not observed in the absence of PEEP, but was first detected during the steady application of 10 and 15 cm H_2O PEEP. In these two cases, there was no obvious relationship between the septal crossing of echo targets and a specific phase of the respiratory or cardiac cycles. In the remaining 30 patients, there was no evidence of interatrial shunt flow during mechanical ventilation without PEEP or with constant PEEP up to 19 cm H_2O. The release of high levels of PEEP, a traditional respiratory maneuver used to provoke interatrial shunt flow in a manner analogous to Valsalva release, failed to permit TEE detection of any additional patients with PFO.

The three patients testing positive for flow-PFO could not be distinguished from the other 30 patients on the basis of anesthetic technique, surgical procedure, airway pressures during mechanical ventilation, or any other monitored variable. Additionally, TEE measurements of right atrial and ventricular dimensions in these patients were within normal limits.

Direct verification of PFO in our patient population was not possible, and thus an estimation of the true

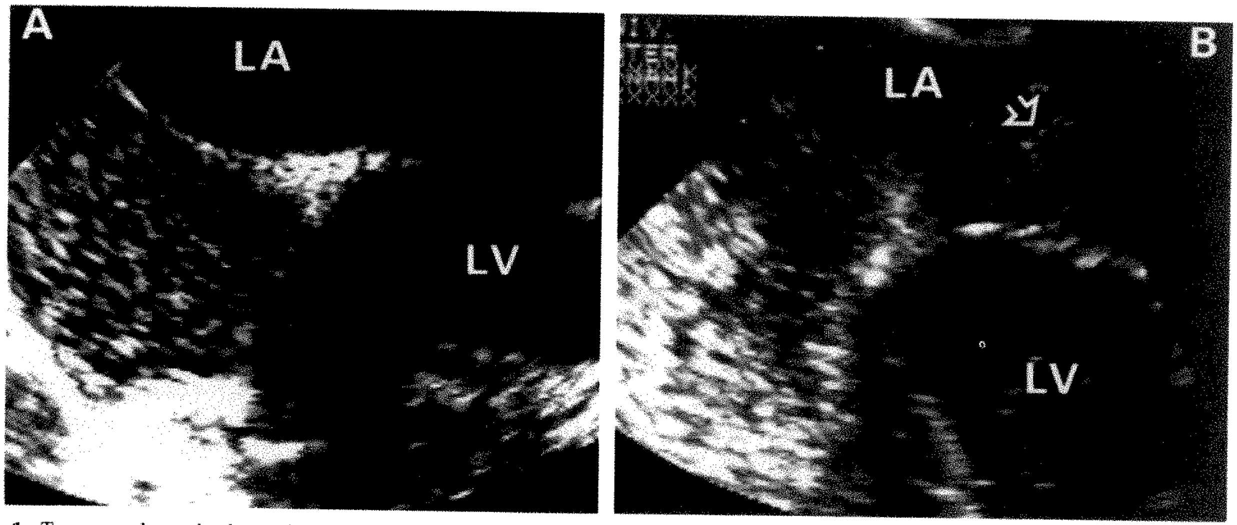

Figure 1. Transesophageal echocardiogram of a patient (**A**) during intermittent positive pressure ventilation and (**B**) during the application of 10 cm of positive end-expiratory pressure. *Arrow*, targets in the left atrium (LA) denoting interatrial shunting; LV, left ventricle. *Unlabeled chambers in the lower left corner* filled with echo targets are the right atrium and right ventricle.

detection rate of TEE for PFO was beyond the scope of this study.

Discussion

The ability to identify patients at risk for paradoxical embolization through a PFO and to characterize specific factors that affect flow through a PFO are of considerable interest to anesthesiologists. Previously reported preoperative screening studies using precordial (transthoracic) echocardiography have been characterized by both low sensitivity and false-negative results (7,14). Contrast imaging with TEE is superior to transthoracic imaging for the detection of PFO (11). Pearson et al. (11) studied 79 patients presenting with unexplained stroke or transient ischemic attacks and compared transthoracic echocardiography with TEE. A PFO was more frequently identified by TEE (9 vs 1 of 79 patients; $P < 0.005$). In a similar study at our institution (12), 4 of 50 patients with recent transient ischemic attack or embolic stroke and normal transthoracic echocardiograms had TEE-detectable PFOs. These findings, confirmed by other investigators (15), demonstrate that contrast two-dimensional (single-plane) TEE is presently the definitive diagnostic technique for PFO detection. The possibility that the single plane of view afforded by two-dimensional TEE may miss crossing echo targets remains of some concern. Recently, biplane and omniplane TEE probes have been introduced into clinical practice (17). Future studies may demonstrate that these devices can enhance the visualization and detection of PFO.

Konstadt et al. (18), in a recently published study of 50 patients with severe cardiovascular disease, using both TEE and Doppler techniques, reported a 26% incidence of *flow*-PFO. These results closely approximate the overall prevalence of *probe*-PFO (25%–27%) from autopsy studies (5,19), and this is the only echocardiographic study to demonstrate this high sensitivity. In the present study, using techniques very similar to those of Konstadt et al. (18), the incidence of flow-PFO in a healthy general surgical population was only 9%. The respiratory maneuver used to provoke shunt flow (release of 19–20 cm H_2O positive airway pressure) was similar in both studies. Konstadt et al. (18) attributed the high detection rate of their TEE technique to four factors that distinguished their study from those previously reported. The first three factors were identical in both studies. Specifically, the heart was imaged using a biatrial view to provide optimal visualization of the interatrial septum (20); second, a vigorous two-syringe technique was used to agitate the saline for the production of high-density microbubble echo targets; and third, complete opacification of the right atrium was assured before a test was considered valid. The fourth factor was their use of pulse-wave and color-flow Doppler techniques. Using these techniques, they were able to detect right-to-left interatrial shunt flow in one additional patient with shunt flow previously undetected by conventional contrast TEE. Overall, however, the color flow Doppler was found to be a much less sensitive technique, detecting only 3 of the 12 patients with right-to-left interatrial shunting (18).

In the absence of any significant technical or operator differences, we believe that the uniquely high detection rate of TEE in the Konstadt et al. (18) study may be related simply to differences in patient populations and the small sample size in both studies. In the present study, only healthy adults undergoing elective nonthoracic surgical procedures were included. In contrast, the Konstadt et al. (18) study patients all had evidence of cardiovascular disease, with 45 of the 50 patients (and 11 of the 12 patients with right-to-left shunt flow) presenting for coronary revascularization or valve replacement, or both. Perhaps myocardial function was altered in these patients in a way that could increase the probability for reversal of the normal left-to-right interatrial pressure gradient or could affect the normal valve characteristics of a probe-PFO. Although these patients should have elevated left atrial pressures, subtle changes in atrial dimensions, myocardial contractility, or conduction pathways may have offsetting effects on the instantaneous interatrial pressure gradient and thus on the functional patency of the foramen ovale.

Anatomic or probe patency, although necessary, may not be sufficient to ensure the physiologic or flow patency of the foramen ovale. The unidirectional flap-valve nature of the foramen ovale requires at least the transient reversal of the normal left-to-right interatrial pressure gradient to permit shunt flow. Persistent reversal of this interatrial pressure gradient is usually associated with right heart outflow obstruction and right atrial volume overload. Transient reversal of the gradient can occur with release of sustained airway pressure (e.g., after a Valsalva maneuver or the release of PEEP). During the strain phase of a Valsalva maneuver or during the sustained application of PEEP, intrathoracic pressure increases, transiently causing right atrial pressure to decrease (secondary to decreased venous return). Then, on release of the Valsalva maneuver or PEEP, venous return to the heart suddenly increases, causing a transient increase in right atrial pressure (as much as 20 mm Hg) (21) with the potential for reversal of the normal interatrial pressure gradient. Langholz et al. (22) recently identified in three patients three different mechanisms for right-to-left flow through a PFO in the absence of elevated pulmonary artery or right atrial pressures: (a) transient reversal of the normal interatrial pressure gradient with each cardiac cycle; (b) preferential streaming of superior vena cava blood entering the right atrium directed at the foramen ovale, producing a localized increase in pressure at that site sufficient to permit shunt flow; and (c) release of 20 cm H_2O PEEP, causing right atrial pressure to increase above left atrial pressure. It is likely that the first two mechanisms operate continuously in all normal persons to at least reduce the magnitude of the interatrial pressure gradient and thus increase the probability of right-to-left shunt flow. For example, in the patient exhibiting the second mechanism described by Langholz et al. (22), the superior vena cava blood flow was directed at the foramen ovale as the result of a large right atrial mass; however, in normal adults, blood returning to the heart via the inferior vena cava is normally directed at the foramen ovale as a persistent anatomic consequence of fetal circulation. Thus, the generation of highly localized atrial septal pressure zones occurs normally but would be difficult to measure by conventional techniques.

The capacity of provocative respiratory maneuvers to cause paradoxical shunt flow may depend simply on the magnitude of the pressure gradient across the foramen ovale at the time of testing. For example, patients with small gradients may exhibit pressure reversals with each respiratory or cardiac cycle (23), whereas in others with large gradients, even the release of 20 cm H_2O PEEP or a Valsalva maneuver may not produce a sufficient increase in right atrial pressure to cause reversal of the normal interatrial gradient.

Somewhat more difficult to explain mechanistically is our observation that the sustained application of PEEP at 10–15 cm H_2O during mechanical ventilation was sufficient to permit right-to-left interatrial shunt flow in all three patients testing positive for flow-PFO using standard respiratory maneuvers. This observation may be explained by hypothesizing that sustained positive airway pressure will eventually increase right atrial pressure relative to left atrial pressure, possibly through an effect on pulmonary vascular resistance, thereby further reducing or reversing the interatrial pressure gradient. Perkins and Bedford (24) reported that right atrial pressure was increased by the application of 10 cm H_2O PEEP and exceeded pulmonary artery wedge pressure (and, by inference, left atrial pressure) in 7 of 11 patients studied while anesthetized in the sitting position. However, more recent studies in both humans (25) and dogs (26) failed to demonstrate any significant effect of 10 cm H_2O PEEP on the absolute interatrial pressure gradient, although 20 cm H_2O PEEP did reverse the interatrial pressure gradient in one of eight patients tested (25). A complete understanding of the factors affecting interatrial pressure gradients will require additional study.

In summary, we have reported the first demonstrations of right-to-left shunt flow evoked as a result of the sustained application of PEEP during general anesthesia. Our results suggest that patients exhibiting intrinsic PEEP or any patient on mechanical ventilation and especially those patients requiring PEEP, such as those in an intensive care unit setting, may be at increased risk for paradoxical embolization after the inadvertent introduction of even small quantities of air at a wound or vascular access site. Furthermore, we would not advocate the use of PEEP in an attempt to decrease the risk of VAE because of the probable increased risk for paradoxical embolization. Finally, we believe that the conventional respiratory maneuvers used to evoke interatrial shunt flow are inadequate in many cases. The ideal provocative maneuver should mimic the changes induced by VAE, specifically producing a sudden increase in pulmonary artery pressure with consequent increase in right heart pressures and subsequent decrease in left heart pressures. Future studies should focus on mechanisms that control the physiologic patency of the foramen ovale. This information will be of considerable clinical importance in the intraoperative and intensive care unit management of many patients.

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Does Adult Liver Transplantation Without Venovenous Bypass Result in Renal Failure?

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Thirty-eight adult orthotopic liver transplant recipients were studied to compare renal hemodynamics and renal function with (17 patients) and without (21 patients) venovenous bypass. Bypass was used when mean arterial blood pressure decreased by >30% or cardiac index decreased by >50%, or both, during a 5-min trial of clamping of the suprahepatic and infrahepatic vena cava and portal vein. Intraoperative measurements were performed 2 h after induction of anesthesia, 10 min before the end of the anhepatic phase, and 2 h after cava unclamping. During the anhepatic stage, renal perfusion pressure decreased significantly in the group with no bypass (79 ± 20 vs 60 ± 17 mm Hg, $P < 0.05$) (mean ± SD), whereas it remained unchanged in the group with bypass (77 ± 14 vs 74 ± 16 mm Hg, NS); urinary output was not modified in the bypass group, whereas it decreased significantly in the group with no bypass compared with the dissection phase (0.7 ± 0.6 vs 1.7 ± 2.0 mL·kg^{-1}·h^{-1}, $P < 0.05$). However, during the postreperfusion phase, urinary output was similar in both groups and was more when compared with the dissection phase ($P < 0.05$). Serum creatinine level was increased in both groups on the third postoperative day, but no difference occurred between the groups (bypass group 107 ± 49 mmol/L; nonbypass group 126 ± 95 mmol/L). No patient required dialysis in either group in the postoperative period. This study suggests that in patients without preoperative renal failure and who tolerate the trial of clamping well, venovenous bypass is not required to maintain postoperative renal function after liver transplantation.

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Advances in surgical technique, anesthetic management, and postoperative care have resulted in improved survival rate after orthotopic liver transplantation (OLT). Among the numerous complications threatening the transplant patient, postoperative renal failure is a frequent and severe event, because it jeopardizes survival (1–3). This may be due to many factors, including intraoperative renal hypoperfusion, sepsis, and administration of potentially nephrotoxic drugs, such as antibiotics and cyclosporine A (2–4). The major blood loss occurring during the perioperative period appears to be an important factor of renal impairment (1), because hemorrhage may result in hypotension and sympathetic vasoconstriction, mainly affecting the afferent glomerular arterioles and causing a decrease in renal blood flow (5). During the anhepatic phase, the increase in inferior vena cava pressure is responsible for a decrease in renal perfusion pressure (6,7). Because a higher incidence of renal failure may occur when venous bypass is not used, its routine use has been advocated to improve early postoperative renal function (8). The aim of this study was to compare renal hemodynamic variations during OLT with and without bypass and to evaluate their consequences on perioperative urinary output and early postoperative renal function.

Methods

During a 5-mo period, 38 adult patients scheduled for a first OLT were studied. This study was approved by our Clinical Research Committee. All patients had normal preoperative renal function, assessed by a serum creatinine (SCr) value <120 μmol/L. Three phases can be identified in the surgical procedure of an OLT. During the dissection phase, the diseased liver is "skeletonized," leaving it with its vascular pedicles intact. The anhepatic phase begins after clamping of all the hepatic vessels; the diseased liver is removed entirely, and the vessels of the donor liver are anastomosed to those of the recipient. When the anastomoses of the portal vein and the vena cava are completed, the vascular clamps are released, and the

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liver is reperfused with portal blood. In our institution, completion of the anastomoses of the hepatic artery and the biliary duct are performed after cava and portal vein reperfusion. All patients were orally premedicated with hydroxyzine (2 mg/kg) 60 min before induction of anesthesia. Anesthesia was induced with thiopental (5 mg/kg) and maintained with a continuous infusion of fentanyl (10 $\mu g \cdot kg^{-1} \cdot h^{-1}$) and midazolam (50 $\mu g \cdot kg^{-1} \cdot h^{-1}$) intravenously. Vecuronium was administered for muscle relaxation. The lungs were ventilated mechanically with a warmed humidified air/oxygen mixture to maintain the end-tidal CO_2 concentration between 30 and 35 mm Hg (Capnomac, Datex), O_2 saturation of arterial blood (Sa_{O_2}) >97%, and pH >7.30. No volatile anesthetic was used. Patients received transfusions of packed red blood cells and fresh-frozen plasma to maintain hemodynamic stability (i.e., mean pulmonary arterial pressure >18 mm Hg or pulmonary artery wedge pressure >12 mm Hg, or both, before the trial of clamping; change in mean arterial pressure <20% during the anhepatic phase) and a hematocrit at 30%. No other fluids (i.e., crystalloids or colloids) were administered during the procedure. Supplemental calcium was administered by infusion to maintain ionized calcium >9 mmol/L. All patients were given 4 g of piperacillin before skin incision and every 8 h for 48 h. For immunosuppression, the administration of prednisolone and azathioprine was begun with the induction of anesthesia (respectively, 5 and 1 mg/kg). In the postoperative period, cyclosporine A was administered intravenously and the dose augmented from 1 to 6 mg/kg.

Monitored variables included mean arterial pressure (MAP [mm Hg]) through a radial artery catheter; thermodilution cardiac index (CI [$L \cdot min^{-1} \cdot m^{-2}$]) through a balloon-tipped pulmonary artery catheter; superior vena cava pressure (mm Hg); inferior vena cava pressure (IVCP [mm Hg]), measured through a 6F 30-cm catheter inserted via the left femoral vein; and renal perfusion pressure (RPP [mm Hg]), calculated as follows: RPP = MAP − IVCP. Intraoperative measurements were made at three times: 2 h after induction of anesthesia (dissection phase), 10 min before the end of the anhepatic phase (anhepatic phase), and 2 h after inferior vena cava (IVC) unclamping (postreperfusion phase). Urinary output (UO [$mL \cdot kg^{-1} \cdot h^{-1}$]) was recorded during each phase of the surgical procedure. The SCr values were measured just before OLT and on the third day after surgery. The administration of blood products was measured at each stage of the operation.

At the completion of the dissection phase, all patients underwent a 5-min test period to determine their hemodynamic response to the clamping of the suprahepatic and infrahepatic vena cava and portal vein. During the next 5 min, the patients were observed for hemodynamic instability, and additional volume was administered to treat hypotension. In patients in whom the test period resulted in a decrease in MAP of >30% or a decrease in CI of >50%, or both, venovenous bypass was utilized to provide hemodynamic support during the anhepatic period. In these patients (n = 17, BP group), the clamps were removed and the bypass cannulas placed in the portal and femoral veins. Blood was pumped from the portal and femoral veins through an extracorporeal circuit without the use of heparin and returned to the left internal jugular vein or the left axillary vein. We used a nonocclusive pump (RP 06 GN, Rhône-Poulenc, Paris, France), the adjustable output of which may in theory be modulated from 0 to 7 L/min. The pump was connected at the end of the dissection phase and disconnected a few minutes after IVC unclamping. Pump flow was continually maximized by the anesthetist, but the blood flow could not be precisely determined, because there was no Doppler flowmeter on the bypass circuit. In the remaining patients (n = 21, NBP group), venovenous bypass was not utilized, and hemodynamic support was maintained by volume administration.

During the surgical procedure, furosemide was administered if the mean pulmonary arterial pressure increased above 35 mm Hg or if oliguria occurred (<1 $mL \cdot kg^{-1} \cdot h^{-1}$ UO). No patient received dopamine during this study.

Statistical analysis was performed with repeated measures analysis of variance followed by appropriate post hoc tests, two-tailed Student's t-test, or Mann-Whitney U-test for normally distributed variables and χ^2-analysis for nonparametric variables. Yates' correction was used when necessary; $P < 0.05$ was considered statistically significant.

Results

Demographic data and diagnosis are reported in Table 1. Age, weight, and preoperative SCr values were similar in the two groups of patients.

Hemodynamic results are listed in Table 2. During the dissection phase, hemodynamic profiles were similar in both the BP group and the NBP group. Likewise, there was no difference in RPP between the two groups. During the anhepatic phase, CI decreased in both groups; superior vena cava pressure decreased in the NBP group when it remained unchanged in the BP group; and IVCP increased with and without bypass. This increase of IVCP was observed throughout the period of IVC clamping and was much greater in the NBP group. Because MAP rapidly returned to preanhepatic values in both groups after IVC clamping, RPP was significantly

Table 1. Clinical Characteristics of 38 Patients Undergoing Orthotopic Liver Transplantation (OLT)

	BP group (n = 17)	NBP group (n = 21)
Gender (M/F)	9/8	19/2
Diagnosis		
Sclerosing cholangitis	1	3
Cirrhosis	13	18
Age (yr)	44 ± 10	41 ± 11
Wt (kg)	65 ± 12	63 ± 10
Preoperative SCr concentration (μmol/L)	72 ± 18	73 ± 13

BP, patients undergoing OLT with bypass; NBP, patients undergoing OLT without bypass; M, male; F, female; wt, weight; SCr, serum creatinine. Mean ± SD.

reduced during all of the anhepatic stage in the NBP group but was not significantly modified in the BP group. During the postreperfusion phase, IVCP and RPP returned to preanhepatic values in both groups.

The UO during the three stages of liver transplantation in the two groups is reported in Table 3. During the dissection phase, UO was similar in both groups. During the clamping period, UO was not modified in the BP group, whereas it significantly decreased in the NBP group. However, during the postreperfusion phase, UO was greater in both groups compared with UO during the dissection phase. No correlations were found between UO and RPP, UO and MAP, or UO and IVCP in either group during any phase of the surgery. It is of note that 11 of 17 patients in the BP group and 14 of 21 patients in the NBP group received furosemide once or many times during at least one phase of the procedure. The number of patients who received furosemide was similar in both groups. Compared with preoperative values, SCr was increased in both groups on the third postoperative day, but this increase was significant only in the BP group. There were no significant differences in SCr between the two groups on the third postoperative day (NBP group 126 ± 95 mmol/L; BP group 107 ± 49 mmol/L), and no patient needed dialysis therapy in the postoperative period. Nine patients in the NBP group and four in the BP group developed a 50% or greater increase in postoperative SCr compared with pretransplant values; however, this difference was not significant.

The duration of the dissection, anhepatic, and postreperfusion phases was similar in the two groups (Table 4). There was no difference between the two groups concerning the total amount of blood products administered during the entire procedure (data not shown). The transfusion of packed red blood cells was similar in both groups during each phase of the surgery. The quantities of fresh-frozen plasma received by the patients were similar during the dissection and postreperfusion phases but were significantly less in the BP group during the anhepatic stage (Table 4).

Discussion

In patients who did not receive bypass support, despite the changes in UO and RPP during the anhepatic phase, no decrement in early renal function could be found compared with the other group in whom UO and RPP had been maintained with the use of bypass.

In our institution, bypass is not used routinely during the anhepatic phase of OLT. We use it selectively in case of fulminant hepatic failure, preoperative renal failure, or when a 5-min trial of venous cross-clamping is not hemodynamically tolerated. The risks of venous bypass should not be neglected. Intraoperative deaths attributable to emboli of air or thrombus have been reported during the bypass period (9). Although embolism remains the most serious hazard of bypass, other problems may occur: longer operative and anhepatic times are inevitable; warm ischemia and the associated risk of graft primary nonfunction may be increased; body temperature may be difficult to maintain (10,11); and local complications, including hematoma, lymphocele, and infection, may also be troublesome. These risks explain why we did not find it ethical to perform a study in which patients who were tolerating the trial of venous cross-clamping well would have been randomly assigned to a group with bypass or to a group without bypass. As such, the two groups are potentially different in their degree of retroperitoneal collateralization and may have received additional collateral flow to their kidneys. Moreover, the two groups may differ in their endogenous reflex responses to acute hypovolemia. Given these restraints and the small number of patients in each group, we cannot definitely conclude that the use of bypass would not improve renal function in the population of patients that did not receive bypass. However, although not randomized, this study is the first that aims at comparing the evolution of renal hemodynamics and renal function during OLT with and without bypass. Of note in our study, we had no accident caused by the use of bypass.

During the anhepatic stage, hemodynamic profiles indicated a lower rate of venous return in both groups, with a higher IVCP and a lower CI, as previously described with and without bypass (6,7,10,12). Thus, even if bypass reduces the hemodynamic changes associated with occlusion of the IVC and portal vein during the anhepatic phase of the transplant procedure, it is likely that bypass was not

Table 2. Hemodynamic Results in Orthotopic Liver Transplantation (OLT) in 38 Patients

Variable	Study group	Dissection phase	Anhepatic phase	Postreperfusion phase
MAP (mm Hg)	NBP	93 ± 17	92 ± 14	90 ± 14
	BP	90 ± 11	94 ± 13	82 ± 18
CI ($L \cdot min^{-1} \cdot m^{-2}$)	NBP	6.0 ± 1.6	3.2 ± 0.9^a	5.7 ± 2.3^a
	BP	5.4 ± 2.1	4.0 ± 1.6^a	4.9 ± 1.6
SVCP (mm Hg)	NBP	10 ± 3	6 ± 5^a	9 ± 3^a
	BP	8 ± 3	12 ± 4^b	10 ± 4
IVCP (mm Hg)	NBP	14 ± 5	32 ± 9^a	14 ± 6^a
	BP	13 ± 5	19 ± 7^{a,b}	13 ± 5^a
RPP (mm Hg)	NBP	79 ± 20	60 ± 17^a	76 ± 13^a
	BP	77 ± 14	74 ± 16^b	69 ± 20

BP, patients undergoing OLT with bypass (n = 17); NBP, patients undergoing OLT without bypass (n = 21); MAP, mean arterial pressure; CI, cardiac index; SVCP, superior vena cava pressure; IVCP, inferior vena cava pressure; RPP, renal perfusion pressure.
Mean ± SD.
$^a P < 0.05$ vs preceding measurement.
$^b P < 0.05$ vs NBP.

Table 3. Urinary Output ($mL \cdot kg^{-1} \cdot h^{-1}$) During the Three Phases of Liver Transplantation in the Bypass (BP) Group and the Nonbypass (NBP) Group

Study group	Dissection phase	Anhepatic phase	Postreperfusion phase
NBP	1.7 ± 2.0	0.7 ± 0.6^a	2.8 ± 1.8^a
(furosemide)	(n = 12)	(n = 1)	(n = 5)
BP	1.5 ± 0.8	1.7 ± 1.6^b	3.2 ± 2.0^a
(furosemide)	(n = 6)	(n = 3)	(n = 7)

Mean ± SD. Numbers in parentheses indicate the number of patients who received furosemide during each phase.
$^a P < 0.05$ vs preceding samples.
$^b P < 0.05$ vs NBP.

totally effective in maintaining venous return. Superior vena cava pressure was decreased only in the NBP group when it was not significantly modified in the BP group; however, MAP and CI variations were similar in both groups between the dissection and anhepatic phases.

As expected, after IVC unclamping, IVCP decreased dramatically in the NBP group and returned to its preanhapatic value. This result is in contradiction with the conclusions of Estrin et al. (7) who found that IVCP was still significantly higher after IVC unclamping than before clamping in a group of 26 adult liver recipients not supported with bypass during the anhepatic phase and in whom MAP was maintained during the anhepatic stage by the use of increasing intravascular blood volume (via a rapid infusion system) and inotropic drugs.

The occurrence of renal failure during or after OLT is a serious event. Thus, in a retrospective study that involved 46 transplant patients, Kirby et al. (1) reported 80% mortality among patients suffering from postoperative renal failure. Although pretransplant renal impairment is not associated with an increased risk of death, a postoperative peak SCr >3 mg/dL (265 μmol/L) would carry a significant risk of death (2). In our study, SCr did not reach this value in any patient. Moreover, the etiology of acute renal failure is a major determinant of patient survival. The most common and serious cause of renal failure after OLT is acute tubular necrosis related to prolonged ischemia associated with sepsis (2,13). Hemorrhage, hypotension from massive blood loss complicated by the vascular instability provides a well-recognized clinical environment in which ischemic renal damage often occurs (14). Renal function is therefore threatened at each phase of OLT. During the anhepatic phase, renal perfusion is notably impaired; indeed, interruption of the IVC produces venous hypertension upstream and venous congestion of infrahepatic structures. Several published studies dealing with the incidence of acute renal failure in adult OLT may be found (2–4). In these, the frequency of acute renal failure varies from 21% (4) to 94.2% (2). This variability in the frequency of renal failure is due at least in part to the criteria chosen to define it. Thus, for Iwatsuki et al. (4), renal failure was defined as the development of a blood urea nitrogen of 50 mg/dL (8 mmol/L) or an SCr of 2 mg/dL (177 μmol/L). For McCauley et al. (2), renal failure was defined as a ≥50% increase in postoperative SCr compared with pretransplant values. Among our patients, 9 of 21 in the NBP group and 4 of 17 in the BP group presented a ≥50% increase in postoperative SCr compared with preoperative values; however, this difference was not significant.

The systematic use of bypass has been suggested to limit the incidence of renal failure after OLT. Nevertheless, it is essential to note that the use of bypass during the anhepatic phase of adult OLT remains controversial. Some transplant centers use bypass routinely (8,10); others never use bypass (7). Shaw et al. (8) found a lower peroperative blood loss

Table 4. Duration of the Three Phases of Orthotopic Liver Transplantation (OLT) and Blood Products Requirements in the Two Groups of Patients

	Dissection phase			Anhepatic phase			Postreperfusion phase		
Study group	Duration (min)	RBC (U)	FFP (U)	Duration (min)	RBC (U)	FFP (U)	Duration (min)	RBC (U)	FFP (U)
NBP	248.2 ± 98.5	4.2 ± 4.0	10.2 ± 7.2	78.9 ± 15.2	1.9 ± 1.7	6.2 ± 4.5	305.1 ± 93.6	3.9 ± 2.5	9.1 ± 6.6
BP	270.0 ± 91.7	2.9 ± 2.7	8.0 ± 3.9	85.6 ± 21.5	1.4 ± 1.3	3.2 ± 2.2[a]	332.0 ± 71.4	5.6 ± 3.2	8.9 ± 6.1

BP, patients undergoing OLT with bypass; NBP, patients undergoing OLT without bypass; RBC, red blood cell requirement; FFP, fresh-frozen plasma requirement.

Mean ± SD.

[a] $P < 0.05$ vs NBP.

and a lower incidence of postoperative renal failure when bypass was used. This they deduced to be due to bypass decompression of the portal hypertension present in the majority of the transplant patients. For other authors, the bypass would not be beneficial in terms of decreasing blood loss during the procedure (15,16). We agree with the latter opinion, because in our study there was no difference between the two groups concerning the total amount of blood products administered during the procedure. The transfusion of packed red blood cells was similar at each phase of the surgery, and the only difference we found concerned the amount of fresh-frozen plasma administered during the anhepatic stage. J. P. Massini et al., in a retrospective study of 33 OLT operations in adults with preoperative SCr <150 μmol/L, found no differences in renal function whether bypass was used or not (communication at the third meeting of the Liver Intensive Care Group of Europe, Brussels, March 1990). In this study, postoperative renal dysfunction was mainly associated with intraoperative difficulties (duration of the anhepatic phase) and blood loss. Finally, we agree with others (15) that bypass is not necessary as a routine during OLT, but it may have a role in patients with compromised cardiac reserve, because it provides better hemodynamic conditions during the anhepatic period of OLT.

Estrin et al. (7) suggested monitoring RPP to maintain it >50 mm Hg during the entire operative period. This 50-mm Hg value might correspond to the lower limit of RPP under which autoregulation of renal blood flow no longer exists. Maintaining RPP >50 mm Hg should allow the renal effect that could be due to the vascular cross-clamping during the anhepatic phase to be limited. In our study, we have recorded RPP values without trying to influence them. During the anhepatic stage, RPP was not modified in the BP group and remained >50 mm Hg in all patients. In the NBP group, during the same period, RPP was significantly reduced and was <50 mm Hg in 8 of 21 patients. Yet, diuresis after IVC unclamping and SCr on the third postoperative day were similar in both groups. Moreover, in the NBP group there was no significant difference in postoperative renal function whether RPP was above or under 50 mm Hg. Thus, RPP monitoring to maintain it above 50 mm Hg during the anhepatic phase may not be needed to preserve renal function. We have now abandoned IVC catheterization for measuring IVCP uniquely. This procedure is not without complications, and during our study one case of a femoral arteriovenous fistula occurred, certainly attributable to the catheter, that required surgery.

In conclusion, this study suggests that in patients without preoperative renal failure and who tolerate the trial of clamping well, the nonutilization of bypass did not result in increased peroperative blood loss or decreased early postoperative renal function. Even if diuresis during the anhepatic phase was more with bypass, postreperfusion UO and SCr values on the third postoperative day were similar, independent of bypass use. At the end of this study the question remains unanswered as to whether patients who did not require bypass after a test period of cava and portal clamping benefit in any way by the routine use of bypass.

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Buccal Pulse Oximeter Is More Accurate Than Finger Pulse Oximeter in Measuring Oxygen Saturation

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Although there have been several anecdotal reports of the use of buccal pulse oximeter monitoring (Spo_2) when digital Spo_2 monitoring cannot be used, there have been no objective evaluations of the accuracy of buccal Spo_2 monitoring. The purpose of this study was to systematically compare buccal Spo_2 monitoring to both digital Spo_2 and arterial O_2 saturation monitoring (Sao_2) in both generally anesthetized patients in the operating room ($n = 31$) and critically ill patients in the intensive care unit ($n = 23$). Buccal Spo_2 probes were prepared by taping a malleable metal bar securely over the back of a Nellcor Oxisensor D-25 probe and bending the metal bar and buccal probe firmly around the corner of the patient's mouth. All buccal and finger Spo_2 and Sao_2 measurements were made simultaneously during hemodynamic stability. We found that buccal Spo_2 was higher than finger Spo_2 and agreed more closely with Sao_2 for both patient groups (98.1% ± 2.6%, 96.8% ± 3.5%, 98.5% ± 2.5%, respectively [mean ± SD]). The operating room patients had higher buccal and finger Spo_2 and Sao_2 (99.3% ± 1.5%, 98.9% ± 1.4%, 99.5% ± 0.7%, respectively) than the intensive care unit patients (96.4% ± 2.9%, 94.1% ± 3.5%, 96.6% ± 3.5%, respectively). Although buccal Spo_2 monitoring has several disadvantages (i.e., the probe requires preparation, can be more difficult to place, may be less readily accepted in awake patients, and is often mechanically dislodged during airway maneuvers), we conclude that buccal Spo_2 monitoring is a more than adequate oximetry alternative when digital Spo_2 monitoring is not an option (digits are unavailable or available digits are mechanically interfered with).

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The use of pulse oximeter monitoring (Spo_2) is now a standard of care in anesthesiology (1). However, the reliability of pulse oximetry probes when applied to the fingers or toes may be compromised in certain patients, such as those who become hypothermic, have decreased cardiac output, have increased systemic vascular resistance, and those who have their extremities or digits mechanically interfered with or who are shivering or moving the monitored digit. As a result, other sites less subject to mechanical interference or a pathophysiologic decrease in pulse amplitude, or both, have been sought, thereby allowing Spo_2 monitoring over a wider variety of surgical and physiologic conditions.

Jobes and Nicolson (2) modified a standard pulse oximeter probe so that it could be attached to the patient's tongue. The hypothesis was that the circulation of the tongue was perhaps more central and therefore better perfused, allowing for more accurate monitoring despite the previously mentioned pathophysiologic factors. In three patients with congenital heart defects who were undergoing cardiac surgery, the tongue sensor functioned well continuously, whereas the peripheral digital sensor functioned only intermittently (one case) or not at all (two cases).

Gunter (3), noting difficulty in keeping the sensor applied to the tongue, modified the probe slightly by attaching a stiffer metal strip to the back of it. He then placed the new metal-backed probe across the lip at the corner of the mouth (i.e., a "buccal" or "cheek" Spo_2 monitor). He noted that the buccal site was always available, very easy to apply, and stayed in place, and without offering any data he concluded that the monitor was reliable even in the presence of arterial vasoconstriction or low cardiac output. Similarly, Sosis and Coleman (4), without reporting any data, monitored buccal Spo_2 by means of an unmodified Ohmeda ear probe. Ezri and colleagues (5) have recently used a probe across the nasal septum with good results.

Although the reports published thus far seem promising (2–4), there have been no formal comparisons of buccal Spo_2 monitoring with digital Spo_2 or arterial oxygen saturation (Sao_2 monitoring). The

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Table 1. Demographic Data of Study Patients

Patient group	Age (yr)[a]	Male	Female	Total
OR	48 ± 20 (10–82)	13	18	31
ICU	43 ± 18 (18–76)	19	4	23
Total	46 ± 19 (10–82)	32	22	54

OR, operating room; ICU, intensive care unit.
[a]Mean ± SD (range).

purpose of this study was to systematically compare buccal Spo$_2$ monitoring to both digital Spo$_2$ and Sao$_2$ monitoring in both generally anesthetized patients in the operating room (OR) and critically ill patients in the intensive care unit (ICU).

Methods

A total of 54 informed, consenting nonsmoking patients were studied: 31 underwent general anesthesia in the OR (OR group), and 23 were monitored in the ICU (ICU group) (Table 1). Patients with indwelling arterial lines (n = 33 [10 in the ICU group, 23 in the OR group]) received simultaneous arterial blood gas analysis (Sao$_2$) with the use of a CO-oximeter 282 (Instrumentation Laboratories, Lexington, Mass.). The buccal mucosa probes were prepared in a manner similar to that described previously by Gunter (3) by taping a malleable metal bar securely over the back of a Nellcor Oxisensor D-25 probe (Nellcor Inc., Hayward, Calif.). Two to three centimeters of the distal tip of the probe were cut off to leave a rounded, tapered end that was easier and less traumatic to insert into the patient's mouth.

All OR-group patients had finger pulse oximeters placed before induction of anesthesia. As soon as it was convenient after induction of anesthesia (generally within 5–10 min), the buccal mucosa probe was placed in the corner of the mouth. Each probe was connected to its own Nellcor model N-100 pulse oximeter. Both machines had been previously checked to ensure that they gave the same reading when attached to the same probe to guarantee that any differences displayed were not due to differences in the sensitivities of each machine. Buccal and finger Spo$_2$ and Sao$_2$ measurements were made simultaneously during a hemodynamically stable postinduction period of anesthesia.

Buccal and finger Spo$_2$ and Sao$_2$ were measured in the mechanically ventilated ICU-group patients during a hemodynamically stable period of time. The probe was placed in the patient's mouth for a few minutes and the readings allowed to stabilize before blood was drawn for blood gas analysis. Once the values were recorded, the probe was usually removed from the ICU-group patient's mouth (some buccal probes were left in for continued monitoring by request of the ICU nurses). One set of observations was obtained in each patient for the purposes of the study.

Table 2. Oxygen Saturation Values in All Patient Groups

Oxygen saturation measurement	Patient group OR	ICU	Total
Sao$_2$	99.5 ± 0.7 (96.9–100)	96.6 ± 3.5 (90.1–100)	98.5 ± 2.5 (90.1–100)
Buccal Spo$_2$	99.3 ± 1.5 (95.0–100)	96.4 ± 2.9 (90.0–100)	98.1 ± 2.6 (90.0–100)
(Pts w/Sao$_2$ reading)	(99.1 ± 1.6)	(97.2 ± 2.5)	(98.4 ± 2.1)
Finger Spo$_2$	98.9 ± 1.4 (95.0–100)	94.1 ± 3.5 (88.0–100)	96.8 ± 3.5 (88.0–100)
(Pts w/Sao$_2$ reading)	(99.0 ± 1.5)	(95.4 ± 3.4)	(97.7 ± 3.0)

OR, operating room; ICU, intensive care unit; Sao$_2$, arterial oxygen saturation; Spo$_2$, pulse oximetry; (Pts w/Sao$_2$ reading), (mean ± SD) buccal and finger Spo$_2$ values for just the patients who had simultaneous Sao$_2$ determinations.

The levels of measurement agreement between finger and buccal sensors as well as between Sao$_2$ and each type of probe were calculated with the method outlined by Bland and Altman (6). The mean difference represents the average difference between each of the data points. Standard error of the mean difference (SEM) was calculated by dividing the standard deviation by $n^{1/2}$, where n = sample size. The limit of agreement represents the mean difference ± 2s (s = standard deviation of the differences). The standard error of the limits of agreement was calculated using the formula $(3s^2/n)^{1/2}$ (6).

Results

Table 2 summarizes the oxygen saturation data in all patient groups. In general, we found that buccal Spo$_2$ was higher on average than finger Spo$_2$ and agreed more closely with Sao$_2$ for all patient groups.

Table 3, which summarizes our statistical analysis, indicates that the buccal Spo$_2$ agreed very closely with Sao$_2$, as shown by the very small mean difference of −0.1% between the two values for all patients, whereas finger Spo$_2$ did not agree nearly as closely with Sao$_2$, with a mean difference of −0.8%. The standard error of limits is similarly smaller in the case of buccal Spo$_2$ versus Sao$_2$ (0.4) compared with finger Spo$_2$ versus Sao$_2$ (0.5). Buccal Spo$_2$ was always higher than finger Spo$_2$ (positive mean difference of 1.2%). We observed the greatest variation between buccal Spo$_2$ and finger Spo$_2$ in patients who had edema in the monitored limb; in patients with severe

Table 3. Summary of Between-Method Statistical Comparisons for the Oxygen Saturation (Spo$_2$) Measurements[a]

Oxygen saturation comparison		Statistical comparison					
Measurement	Patient group	*n*	Mean difference (%)	s	SEM	Limits of agreement	Standard error of limit
Buccal Spo$_2$ vs finger Spo$_2$	OR	31	0.3	1.56	0.3	3.4 to −2.8	0.5
	ICU	23	2.3	2.24	0.5	6.8 to −2.1	0.8
	Total	54	1.2	2.13	0.2	5.4 to −3.1	0.3
Buccal Spo$_2$ vs Sao$_2$	OR	23	−0.5	1.21	0.3	2.0 to −2.9	0.4
	ICU	10	0.6	1.59	0.5	3.8 to −2.5	0.9
	Total	33	−0.1	1.41	0.3	2.7 to −2.9	0.4
Finger Spo$_2$ vs Sao$_2$	OR	23	−0.5	1.15	0.2	1.7 to −2.3	0.4
	ICU	10	−1.2	2.12	0.7	3.0 to −5.4	1.2
	Total	33	−0.8	1.57	0.3	2.4 to 3.9	0.5

SEM, standard error of the mean difference; s, standard deviation of the differences; OR, operating room; ICU, intensive care unit.
[a]Statistical comparisons for buccal and finger Spo$_2$ vs Sao$_2$ are only for the patients who had simultaneous paired determination.

edema, the difference was as much as a positive 5%–6%. The reader may note that in Table 3 (comparisons of the two probes with Sao$_2$), the mean difference represents only those patients who had Sao$_2$ analysis. In Table 2, the average readings of these patients as well as of the entire patient population are given.

On average, the ICU-group patients had lower oxygen saturation than did the OR-group patients (Table 2). Both buccal Spo$_2$ and finger Spo$_2$ were less accurate relative to Sao$_2$ in the ICU-group patients compared with the OR-group patients, as evidenced by the larger mean difference and limits of agreement for the ICU versus the OR group (Table 3). However, the buccal Spo$_2$ is also statistically closer to Sao$_2$ in the ICU group than the finger Spo$_2$, as demonstrated by the buccal Spo$_2$ versus Sao$_2$ mean difference of 0.6% compared with the finger Spo$_2$ versus Sao$_2$ mean difference of −1.2%. Similarly, the buccal Spo$_2$ versus Sao$_2$ mean difference for the ICU group is 0.625 (limit of agreement of 3.8 to −2.55), whereas the finger Spo$_2$ versus Sao$_2$ mean difference is −1.2 (limits of agreement of 3.04 to −5.44) for the ICU group.

Discussion

Our main objective in performing this clinical study was to determine whether buccal Spo$_2$ monitoring was at least as accurate as finger Spo$_2$ monitoring relative to simultaneous Sao$_2$ monitoring. We found that buccal Spo$_2$ was more accurate than finger Spo$_2$ relative to measured Sao$_2$. We did not correct measured Sao$_2$ with levels of methemoglobin and carboxyhemoglobin, because we were looking for a relative standard to measure each of the two probes against. Although it is conceivable that the levels of methemoglobin and carboxyhemoglobin could account for some of the difference between Sao$_2$ and Spo$_2$ measured at the buccal and digital sites, the difference is a constant because all readings were made simultaneously. In the absence of smoking (minimal carboxyhemoglobin and methemoglobin levels), simultaneous Sao$_2$ is a relevant control saturation.

We chose not to analyze our data with correlation coefficients that were generated by linear regression based on the arguments presented by Bland and Altman (6); the argument includes the fact that there will be perfect agreement only if all of the data points lie along a line of equality, but there can be perfect correlation if the points lie along any straight line. This point is demonstrated by Ezri et al. (5) who found nearly identical correlation coefficients between nasal septum Spo$_2$ and Sao$_2$ (0.968) and finger Spo$_2$ and Sao$_2$ (0.970), even though there were very different mean differences (0.15 vs 2.27, respectively) and limits of agreement (−0.1 to 0.4 vs 2.0 to 2.6, respectively) between the two measures of oxygen saturation. We instead compared the values produced by two different measuring devices by a direct between-method differences analysis. The limits of agreement are only estimates of the value that apply to the whole population. The standard error is used to determine how precise the estimates are; the smaller the standard error, the more accurate the estimate is for the population (6).

We found that buccal Spo$_2$ was always higher than finger Spo$_2$ and agreed more closely with Sao$_2$, even in conditions where differences between measurement methods were increased (i.e., the more hypoxemic ICU group). It may be that buccal pulsations are stronger under a wider variety of clinical conditions and result in more accurate oximeter saturation readings. Coupled with its high incidence of availability, the accuracy of the buccal Spo$_2$ makes it an attractive alternative to finger Spo$_2$ monitoring.

If the magnitude of the Spo_2 limits of agreement is clinically unimportant, the devices would be interchangeable. In this study we found that buccal Spo_2 versus Sao_2 had limits of agreement of 2.75 to −2.88. The finger Spo_2 versus Sao_2 had limits of agreement of 2.35 to −3.92. It could be argued that these levels of difference are clinically irrelevant, thereby making either device a satisfactory method of monitoring the patient's oxygenation. Although the buccal site does not represent a marked improvement, it is slightly more accurate by our calculations. An anesthesiologist can therefore be assured that the readings observed with a buccal probe are an accurate indication of the patient's oxygen saturation status.

We encountered four major technical difficulties in applying buccal Spo_2 monitoring. First, the buccal probe is less well accepted in awake patients compared with the finger probe. Second, the buccal probe can be displaced or interfered with during ventilation of the patient through an anesthesia mask and during laryngoscopy. Third, given the usual (normal) unrestricted exposure to the extremity and the corner of the mouth, it is initially somewhat more time consuming to prepare and place a buccal probe compared with a finger probe. Fourth, in the lateral decubitus position, saliva may accumulate over time, making it difficult to maintain probe position on the dependent corner of the mouth. This problem can be solved by placing the probe on the upper corner of the mouth or by administering an anticholinergic agent to reduce saliva production.

In conclusion, the use of buccal Spo_2 monitoring makes sense for several reasons. First, the corner of the mouth is usually readily accessible to the anesthesiologist, whereas the digits are often remote or made inaccessible by the surgical drapes or the patient's position. Second, in patients who have burns or other serious injury to their hands and feet, the buccal mucosa may be the only available site for pulse oximetry monitoring. Third, the buccal Spo_2 values are accurate (compared with simultaneous Sao_2). Indeed, it appears that the circulation to the buccal mucosa is less subject to peripheral vasoconstriction and decreased pulse amplitude than are the peripheral sites used for pulse oximetry, such as the fingers and toes. Therefore, the anesthesiologist using buccal Spo_2 monitoring, either from convenience or necessity, can be confident that the readings are at least as accurate as the commonly used finger probe in determining the patient's level of oxygen saturation.

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Recognition Accuracy of Current Operating Room Alarm

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This prospective study was performed to determine whether anesthesia clinicians (i.e., both anesthesiologists and nurse anesthetists) can identify operating room alarms by their distinctive sounds and to identify factors related to alarm recognition accuracy. Nineteen alarms from 15 commonly used devices were recorded. These sounds were played, in a quiet room, to 44 anesthesia clinicians. The clinicians were asked to choose from a list the device that produced the alarm. After this recognition test, the clinicians rated the importance of each alarm and the frequency with which they heard it in the clinical situation. Clinicians correctly identified the alar source 34% of the time. The recognition rate wa higher for alarms rated as heard more frequently however, alarms that were rated as more importan were *less* likely to be correctly identified. Complexit of the sound did not influence accuracy of recognition. Most errors were attributed to similarities i sound or function, or both, among alarms. We conclude that anesthetists cannot reliably identify current operating room alarms by their distinctiv sounds.

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Modern operating rooms are filled with devices that generate audible alarms intended to alert the clinician to potentially hazardous conditions. It is therefore important that the clinician be able to quickly identify any alarm, because the inability to do so can delay or prevent the appropriate corrective action (1).

The three criteria for determining the effectiveness of audible alarms are audibility, attention demand, and recognition (2). Audibility refers to whether a sound can be heard in the presence of typical background noise. Attention demand is a measure of whether an unexpected alarm will be perceived. Recognition implies that the sound will be interpreted as an alarm and that its meaning will be understood.

Noise-level readings taken during typical operations have established the fact that the operating room is indeed a noisy environment, comparable to that of a freeway (3,4). Even so, audible alarm signals that can be reliably detected above operating room noise levels have been identified (5). Stanford et al. (5) concluded that signals with spectral richness, frequency modulation, and temporal patte could be reliably detected amid operating equipment noises in a laboratory setting.

There are anecdotal reports of difficulty in i fying the source of an alarm in the clinical en ment (6,7). A presumed reason is that many a have similar sounds; yet, of 852 Canadian an tists responding to a survey, half (422) indicate the distinctiveness of the alarm sound was useful in determining its source than was eith direction of the sound source or a visual indicat The aim of our study was to measure anes clinicians' ability to identify the source of fa alarms by sound characteristics alone. We also i tigated the factors that influence alarm recogni

Methods

Nineteen alarm sounds from 15 devices in our ating rooms were digitally recorded at 22 Hz 8-bit resolution. The volume of each alarm wa measured with a precision sound-level meter (2209, Brüel and Kjaer Instrumentation Co., Ma ough, Mass.) (A scale). Each volume measure was performed from the head of the operating table and at a height of 4 ft, with the device typical location and set at its default volume The volume of each recorded alarm, played th headphones, was then adjusted to that of the or

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alarm by means of the sound-level meter and a commercial software program (SoundEdit 1.0, Farallon Computing, Berkeley, Calif.). The complexity of each alarm sound was rated by an audiologist who was unfamiliar with the operating room. She classified each as continuous tone, intermittent tones separated by periods of silence, or multitone.

Our institutional review board granted approval, and all subjects consented to the study. Twenty-three anesthesia residents, 12 anesthesia attending physicians, and nine certified registered nurse anesthetists (CRNA) participated. Each of the subjects routinely used all of the devices from which the alarms were recorded.

Each subject was tested while seated in a quiet room. The subject's hearing was screened at 1000, 2000, 3000, and 5000 Hz, and deficits >30 dB were noted. After the hearing test, the subject heard the recorded alarm sounds through calibrated headphones. The alarms were presented in random order, and each was presented twice during the session. The subject was asked to select from a list the device that generated the alarm sound. The list contained one entry for each of the 15 devices and an entry named "Don't know." Each entry listed the type of device, the manufacturer, and a short description of the device's appearance. Subjects received the following written instructions:

> Each alarm will sound for 17 seconds and will be followed by 10 seconds of silence. You should verbally identify the monitor which generates the alarm as soon as you can during the 27 seconds after the alarm begins to sound. If you have not responded after the 27 seconds have elapsed, you will be asked to either identify the monitor or indicate that you "don't know".

After the alarm recognition test, each subject was given a list of the 19 alarm sounds and was asked to indicate for each (a) how important the alarm is in clinical practice (critical, important, or advisory); and (b) how frequently, in his or her experience, the alarm occurred (frequently, infrequently, or rarely). Two demographic items were collected for each subject: (a) clinical training (resident, faculty, or CRNA); and (b) clinical experience (number of years since beginning anesthesia training).

Data are expressed as frequencies of correct recognitions. Comparisons between groups of alarm importance and frequency of alarm occurrence were by χ^2 analysis. The correlation between each clinician's rating of alarm importance and frequency of alarm occurrence was analyzed with Spearman rank correlation. Least-squares regression was used to determine the effects of clinical experience and alarm volume on recognition rate. Tests were performed with Data Desk version 3.0 (Odesta Corp., Northbrook, Ill.). A value of $P < 0.05$ was considered significant.

Results

Forty-four anesthesia clinicians heard each of 19 alarms twice, providing a total of 1672 responses. Table 1 presents the frequencies of responses for each alarm sound. The correct responses are outlined on the main diagonal. The alarm sounds were correctly identified 571 times (34%) and incorrectly identified 843 times (50%); clinicians admitted to not knowing the correct answer 258 times (16%).

The clinician with the best performance, a new resident, identified 26 alarms correctly (68%); the worst performance, by a clinician with 26 years' experience, was three correct (8%). There was no correlation between a subject's clinical experience and his or her ability to correctly identify alarms (Figure 1). Hearing deficits were detected in six subjects. The scores of the clinicians with hearing deficits were not different from those with normal hearing.

On the questionnaire, clinicians judged the tested alarms as critical 37% of the time, important 34% of the time, and advisory 29% of the time. When clinicians rated an alarm as more important, it was less likely that they would correctly identify it (Figure 2). Alarms were rated as being frequently, infrequently, and rarely heard 30%, 30%, and 41% of the time, respectively. The more frequently clinicians believed that they heard an alarm, the more likely it was that they would identify it (Figure 3). For each clinician, there was a negative correlation between how important he or she thought the alarm was and how frequently he or she thought that it was heard. The alarms believed to be less important were judged to be heard more frequently.

The alarm with the highest recognition rate (Fisher & Paykel humidifier) was correctly identified 92% of the time, whereas that with the lowest recognition rate (Ohmeda 7000 Ventilator power failure) was correctly identified only 1% of the time. Six of the alarms were continuous tones, five were intermittent tones separated by periods of silence, and eight were multitone. Sound complexity did not affect recognition rate; however, there was a positive correlation between alarm volume and recognition rate ($P < 0.01$) (Figure 4).

Table 1 presents the frequencies of responses for each alarm sound. The correct responses are outlined on the main diagonal. Entries outside the main diagonal and the "Don't know" column are mismatches; these may have occurred owing to confusion or chance. Mismatches due to random chance would result in a cell frequency of

Table 1. Clinicians' identification of alarm sounds, grouped by sound categories. Correct responses are outlined on the *main diagonal*. Relevant confusions are in *bold type*. *Shading* indicates a sound pattern similarity between the device on the horizontal axis and the one on the vertical axis.

SOUND \ RESPONSE	Line Isolation Monitor	Alfenta Pump	Nellcor	Electrocautery	Ventilator	MiniOx Oxygen	Ohmeda Oxygen	SARA	Datex AGM	Volumeter	Airway Pressure	Anesthesia Machine	Dinamap	Puritan Bennett	Humidifier	Don't know	Total
Line Isolation Monitor	**52**	**2**		**19**	1		1								1	12	88
Bard Alfenta Pump	**9**	**9**	**6**	**30**		3	2	1	1		3	1	1		1	21	88
Nellcor Pulse Oximeter	**9**	3	**7**	**33**		4	4	1	1		1	1		1		23	88
ValleyLab Electrocautery	1	**6**	1	**25**	**22**		1	2	2	5	**8**	3			4	8	88
Ohmeda 7000 Ventilator (disconnect)	1	**6**	1	2	**29**	3	**6**	3	1	5	**14**	2			4	11	88
Ohmeda 7000 Ventilator (power failure)	5	**7**	2	**6**	1	**23**	**12**	**6**	2		2	4				18	88
Miniox Oxygen Analyzer		3	1		**6**	**43**	**11**	5	1	1	3	1			3	10	88
Ohmeda Oxygen Analyzer		**9**	2	5		**7**	**11**	**6**	**10**	**6**	**7**		1	2	1	21	88
SARA Mass Spectrometer		**6**		1	4	3	**8**	**33**	5	4	5			4	2	13	88
Datex Airway Gas Monitor		**10**		2	2	**8**	**6**	**16**	**14**	3	**10**	2		2		13	88
Ohmeda Volumeter (threshold)	1	3	3	2	3	1	**9**	**10**	**9**	**22**	**6**			1	4	14	88
Ohmeda Volumeter (apnea)	1	1	2		**10**	1	**7**	4	4	**17**	**16**	5	**9**	2	**7**	2	88
Ohmeda Airway Pressure			2	1	**10**	1	**8**	**7**	5	**15**	**17**	1	1	5	5	10	88
Ohmeda Modulus I (low oxygen pressure)	**10**				1		1				**11**	**40**				25	88
Ohmeda Modulus II (power failure)	1	2	1	**9**	**6**		2		3	4	**11**	**7**	**14**	1	3	24	88
Dinamap (technical)		1	1	**10**	**11**	1		1		5	4	1	**33**		2	18	88
Dinamap (threshold)	1	1	2		1	1		3		1	4		**69**		2	3	88
Puritan Bennett Multifunction		2	1	1				**6**	2	1		3		**61**		11	88
Fisher & Paykel Humidifier							1			1	1	2		1	**81**	1	88
Total	91	71	32	146	107	99	90	104	60	90	123	73	128	80	120	258	1672

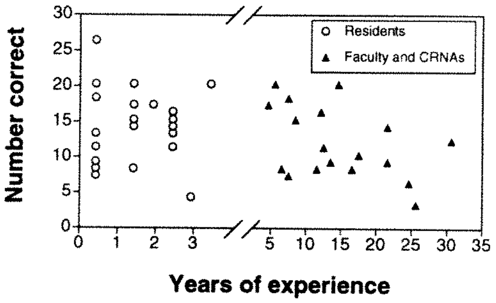

Figure 1. Number of alarm sounds correctly identified (of 38) versus the clinician's years of anesthesia experience.

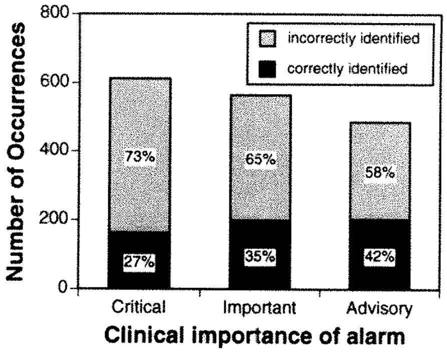

Figure 2. Number of correctly and incorrectly identified alarm sounds versus the clinician's rating of the alarm's clinical importance. There is a significant difference between groups ($P < 0.0001$).

[(No. of times that each alarm sound was presented) − (No. of "Don't know" responses)] ÷ (No. of possible responses)

or

[88 − (No. of "Don't know" responses)] ÷ 15

for each row. Cell frequencies that exceed this threshold indicate a relevant confusion (9). Interpreted in this way, 571 responses were correct (34%), 573 were relevant confusions (34%), 258 were "Don't know" (16%), and 270 were random mismatches (16%).

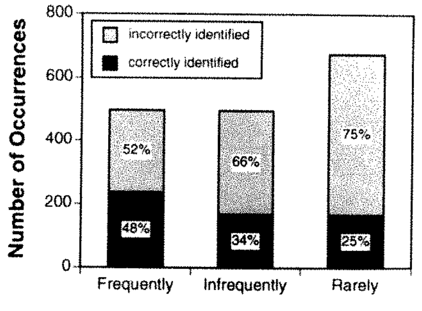

Figure 3. Number of correctly and incorrectly identified alarm sounds versus how frequently the clinician hears the alarm in clinical practice. There is a significant difference between groups ($P < 0.0001$).

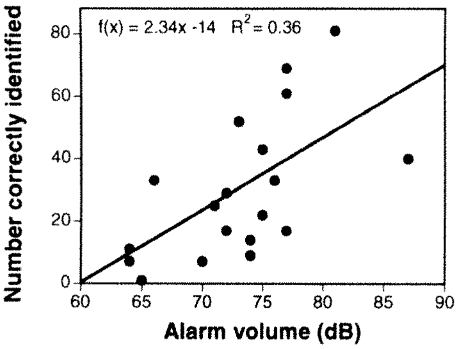

Figure 4. The number of times an alarm was correctly identified versus the alarm volume. Each alarm was presented 88 times, twice each to 44 subjects. The linear regression line is significant at $P < 0.01$.

Discussion

The data indicate that anesthesia clinicians cannot determine the source of current commercial operating room alarms solely by sound characteristics. This contradicts the subjective impression (8). The study does not imply that alarms cannot be identified quickly in the clinical setting. During clinical use, identification may be facilitated by visual indicators on the monitor, the direction from which the sound is produced, and interpretation of the clinical scenario at the time of the event.

Alarm recognition in the operating room is hampered when each device has a proprietary alarm sound. This is due to a number of factors. First, numerous sounds must be recognized. We identified 19 audible alarms in the operating rooms at our institution. Second, alarms may occur simultaneously. Third, the user may rarely use a particular device and thus infrequently hear a particular alarm. Experiments by Patterson and Milroy (10) indicate that subjects can readily learn to recognize four to six audible alarms, and 1 wk after learning 10 alarms, subjects can reliably recognize only six. This is consistent with other studies that demonstrate the limitations of humans in differentiating among multiple stimuli (11). It suggests that the number of alarm sounds should be reduced to a maximum of six. The number of sounds can be decreased in two ways: standardization of sounds and limitation of alarms. Standardized alarms could reduce the total number of sounds and would ensure that unfamiliar equipment had familiar alarms. Limiting the use of audible alarms would reduce the total number of sounds and the chance of simultaneous alarms. Eventually, integrated monitoring systems with centralized alarms would be ideal, but in the interim, the situation could be improved by standardizing audible alarms and limiting their use.

It is intuitive that the most important alarms should have sounds that are most easily identified by anesthesiologists; however, we found an inverse relationship between alarm importance and recognizability. For example, the Fisher & Paykel humidifier alarm had a low importance rating but was very well recognized. This alarm is loud, continuous, and has a complex sound pattern. These features may elicit a strong affective response in the anesthetist that may increase recognition. A related study by Finley and Cohen (12) found no correlation between the perceived urgency of commercial operating room alarm sounds and the urgency of the clinical situation. Thus, there is accumulating evidence that current commercial auditory alarms are poorly correlated to the situations of which they are warning.

Although our study demonstrates a problem with the current unstructured approach to alarms, it provides little data to guide manufacturers in developing more recognizable alarms. There was a positive correlation between alarm volume and recognition rate; however, we do not recommend that alarm volumes be increased indiscriminately. An anesthesiologist's initial response might be to silence a louder alarm rather than address the clinical problem that caused it. Also, louder alarms would be more disruptive to the rest of the operating room team. We presumed that the more complex alarm sounds would be better recognized, but our data do not support this conclusion. Additional research is needed to develop alarm sounds that are recognizable and detectable but not disruptive. The more urgent and recognizable sounds should be reserved for the more important alarms, and before general use, the sounds should be evaluated in operating rooms to determine their effect on personnel performance.

We looked for patterns of recognition errors in our data to understand the processes involved in recognizing alarm sounds. This method has been used previously to investigate factors that affect other

Table 2. Alarm Sound Categories

Category description	Alarm category
Continuous	
Broadband	Line Isolation Monitor Nellcor Pulse Oximeter Bard Alfenta Pump Buzzing of Electrocautery[a]
Distinct tone	Ohmeda 7000 Ventilator (power failure) Miniox Oxygen Analyzer
Broadband, siren	Ohmeda Modulus I (low oxygen pressure)
Intermittent tone	
Approximate cycle time of 1 s	Ohmeda Oxygen Analyzer Ohmeda Volumeter (threshold) Ohmeda Volumeter (apnea) Ohmeda Airway Pressure SARA Mass Spectrometer Datex Airway Gas Monitor
Approximate cycle time of 0.3 s	Ohmeda 7000 Ventilator (disconnect) ValleyLab electrocautery
Burst of intermittent tone separated by long pause	Dinamap (threshold) Dinamap (technical) Ohmeda Modulus II (power failure)
Greater than two tones (these two not similar to each other)	Puritan Bennett Multifunction Fisher & Paykel Humidifier

[a] Even though it is not an alarm, the "buzzing" sound of electrocautery was included in this category. See text for explanation.

recognition tasks (9). We were most interested in understanding the relevant confusions, because these signify systematic errors in the interpretation of the alarm sounds. Retrospective review of the data suggested that many mismatches resulted from two underlying causes: (a) sound confusion and (b) function confusion. The first, sound confusion, was a mismatch between alarms with similar sound qualities. We retrospectively classified the alarms by similarity of sound into seven categories (Table 2). Table 1 is grouped by sound categories to highlight the areas of potential confusion. An example of sound confusion is the 14 responses of "Dinamap" to the Ohmeda Modulus II power failure alarm. The Modulus and Dinamap alarms sound similar; both are complex sounds with a burst of patterned tones separated by long periods of silence. Another example is the 33 responses of "electrocautery" to the Nellcor pulse oximeter alarm. This alarm is a constant, broadband sound that is similar to the "buzzing" of electrocautery. There were 327 relevant confusions that we believed could be attributed, at least in part, to sound confusion.

The second cause of mismatches was function confusion. This occurred when the subject attributed an alarm to another piece of equipment with a similar clinical function. Each alarm was classified as being in one or more of the following function categories: gas concentration, pressure, circuit disconnect, power loss, oxygenation, ventilation, circulation, and temperature. Table 3 displays our data grouped by function categories to highlight the areas of potential confusion. Examples are the confusions among the gas analyzers: the Miniox oxygen analyzer, the Ohmeda oxygen analyzer, the Datex airway gas monitor, and the SARA mass spectrometer. Another function confusion, which may be more difficult to appreciate, is the anesthetist's response of "airway pressure" to the Ohmeda Modulus I low-oxygen-supply pressure alarm; however, these are both pressure alarms. There were 202 relevant confusions that we believed could be attributed, at least in part, to function confusion.

In this retrospective analysis of relevant confusions, 36% were due to sound confusion, 15% to function confusion, 21% to both, and 28% to neither. Function confusions suggest that clinicians mentally group alarm sounds by monitor function. This may be advantageous in the clinical environment, because attention is directed to the appropriate system. It also reinforces the position that alarm sounds should be grouped by function (13). Our results indicate that the recognition rate for the alarm's function could be readily increased to 55% (the number of correct responses plus the number of relevant confusions due to function confusion) if alarms with similar functions had similar sounds.

Table 3. Clinicians' identification of alarm sounds, grouped by function categories. Correct responses are outlined on the *main diagonal*. Relevant confusions are in *bold type*. *Shading* indicates a functional similarity between the devices on the vertical and horizontal axes.

SOUND \ RESPONSE	Line Isolation Monitor	Alfenta Pump	Electrocautery	Anesthesia Machine	Volumeter	Ventilator	Airway Pressure	SARA	Datex AGM	MiniOx Oxygen	Ohmeda Oxygen	Nellcor	Dinamap	Puritan Bennett	Humidifier	Don't know	Total
Line Isolation Monitor	**52**	2	**19**			1					1				1	12	88
Bard Alfenta Pump	**9**	**9**	**30**	1			3	1	1	3	2	**6**	1		1	21	88
ValleyLab Electrocautery	1	**6**	**25**	3	5	**22**	**8**	2	2		1	1			4	8	88
Ohmeda Modulus II (power failure)	1	2	**9**	**7**	4	**6**	**11**		3		2	1	**14**	1	3	24	88
Ohmeda Modulus I (low oxygen pressure)	**10**			**40**		1	**11**				1					25	88
Ohmeda Volumeter (threshold)	1	3	2		**22**	3	**6**	**10**	**9**	1	**9**	3		1	4	14	88
Ohmeda Volumeter (apnea)	1	1		5	**17**	**10**	**16**	4	4	1	**7**	2	**9**	2	**7**	2	88
Ohmeda 7000 Ventilator (disconnect)	1	**6**	2	2	5	**29**	**14**	3	1	3	**6**	1			4	11	88
Ohmeda 7000 Ventilator (power failure)	5	**7**	**6**	4		1	2	**6**	2	**23**	**12**	2				18	88
Ohmeda Airway Pressure			1	1	**15**	**10**	**17**	**7**	5	1	**8**	2	1	5	5	10	88
SARA Mass Spectrometer		**6**	1		4	4	5	**33**	5	3	**8**			4	2	13	88
Datex Airway Gas Monitor		**10**	2	2	3	2	**10**	**16**	**14**	**8**	**6**			2		13	88
Miniox Oxygen Analyzer		3		1	1	**6**	3	5	1	**43**	**11**	1			3	10	88
Ohmeda Oxygen Analyzer		**9**	5		**6**		**7**	**6**	**10**	**7**	**11**	2	1	2	1	21	88
Nellcor Pulse Oximeter	**9**	3	**33**	1			1	1	1	4	4	**7**		1		23	88
Dinamap (technical)		1	**10**	1	5	**11**	4	1		1		1	**33**		2	18	88
Dinamap (threshold)	1	1			1	1	4	3		1		2	**69**		2	3	88
Puritan Bennett Multifunction		2	1	3	1			**6**	2			1		**61**		11	88
Fisher & Paykel Humidifier				2	1		1				1			1	**81**	1	88
Total	91	71	146	73	90	107	123	104	60	99	90	32	128	80	120	258	1672

Our study has a number of potential design flaws. First, recorded alarms were used rather than the sounds from the actual machines. However, the investigators compared high-quality cassette recordings and digital recordings with the original sounds and believed that the digital system had superior playback sound quality. Even so, any sound recording and playback has the potential for distortion, and 13 of the subjects believed that the quality of the recordings interfered with their ability to recognize at least some of the alarms.

Second, the 19 alarms that we recorded would not all be present during a single operative case. Although all of the devices are used at our institution, there are variations in equipment among operating rooms. For example, we tested the alarms from two different oxygen analyzers, although only one model would be used in any single case. This artificially increased the number of possible alarms and may have interfered with the use of a situational factor in the recognition of alarms. Experienced clinicians anticipate foreseeable problems better than trainees do (14). Thus, a situational factor may be used by the experienced clinician in that he or she may expect particular alarms at certain phases during the course of an operation or may not consider alarms from equipment not currently in use. There may also be other factors, such as stage of the operation or patient illness, that cue the experienced clinician to particular monitors and alarms.

We conclude that current operating room alarms cannot be reliably recognized by sound characteristics alone. Some sounds are better recognized than others, and anesthetists mentally group alarm sounds by function.

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Variation in Arterial to End-Tidal CO_2 Tension Differences During Anesthesia in the "Kidney Rest" Lateral Decubitus Position

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The course of arterial to end-tidal carbon dioxide tension difference [$P(a\text{-}ET)CO_2$] was evaluated during general anesthesia in 25 patients scheduled for renal surgery performed in the "kidney position." The difference between arterial PCO_2 ($PaCO_2$) corrected to body temperature, and end-tidal PCO_2 ($PETCO_2$) measured by mass spectrometry was assessed after induction of anesthesia, after placement in the lateral decubitus position with back arched over a kidney bridge ("kidney position"), and every 20 min until the patients were replaced in the supine position at the end of the surgical procedure. Heart rate, arterial blood pressure, and esophageal temperature were simultaneously recorded. After induction of anesthesia, when the patients were lying supine (T1), $P(a\text{-}ET)CO_2$ was 4.8 ± 3.9 mm Hg (mean ± SD). Placing the patients in the kidney position (T2) induced a significant increase in $P(a\text{-}ET)CO_2$ (to 7.9 ± 3.5 mm Hg; $P < 0.01$). These alterations occurred without any significant change in mean arterial blood pressure or heart rate. A progressive increase in mean $P(a\text{-}ET)CO_2$ occurred with maintenance of anesthesia; $P(a\text{-}ET)CO_2$ reached 8.8 ± 4.1 mm Hg ($P < 0.05$ vs T2) and 8.9 ± 4.4 mm Hg ($P < 0.05$ vs T2) at 65 and 85 min, respectively, after lateral decubitus positioning. Large variations between and within patients were observed. Although stable mean arterial pressure was maintained, these changes were associated with a significant decrease in body temperature. These results demonstrate that $P(a\text{-}ET)CO_2$ increases when patients are placed in the kidney position and may vary with the prolongation of anesthesia in this situation. Thus, $PETCO_2$ can be affected by position, and thus may not be constantly of value when estimating $PaCO_2$ during anesthesia.

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The monitoring of expired carbon dioxide concentration is becoming increasingly commonplace in the operating room. Intraoperative mishaps, such as inadvertent esophageal intubation, valve dysfunction, or disconnection from the ventilator, may be accurately detected with capnography (1–3). Moreover, measurement of end-tidal partial pressure of carbon dioxide ($PETCO_2$) has been recommended for the noninvasive estimation of $PaCO_2$ (4–6). Especially during anesthesia, $PETCO_2$ generally underestimates $PaCO_2$ (7,8), and the arterial to end-tidal difference $P(a\text{-}ET)CO_2$ varies between patients (8,9). The $P(a\text{-}ET)CO_2$ value depends on the alveolar dead space, which in turn is mainly influenced by the relative distribution of ventilation and perfusion (V/Q) within the lungs (10). Changes in these variables can induce variations in $P(a\text{-}ET)CO_2$. Patients scheduled for renal surgery via the lateral decubitus position are lying on their sides arched over a "kidney bridge," and the hips are somewhat flexed. We hypothesized that this kidney position could alter the $P(a\text{-}ET)CO_2$ value. Lateral decubitus positioning is known to impair ventilation/perfusion relationships in anesthetized patients (11,12). Further, the bridge may decrease venous return and increase the physiologic dead space (13). These alterations probably modify the $P(a\text{-}ET)CO_2$ difference, but this phenomenon has not been investigated.

Stability of arterial to end-tidal gradients within individual patients throughout a surgical procedure remains controversial. Some authors did not identify large modifications during maintenance of anesthesia (4,14), whereas others reported important variations within individual patients (15–17). These variations have been demonstrated in situations, such as cardiac and aortic surgery (15,16) or laparoscopy (17), where important disorders in hemodynamic status

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or CO_2 production, respectively, occur. The course of P(a-ET)CO_2 during maintenance of anesthesia is not well characterized in patients who do not undergo such intraoperative hemodynamic alterations (13,14) but are subjected to potentially physiologically disruptive positions during surgery.

Therefore, the aims of this study were to determine the consequences of the kidney position on P(a-ET)CO_2 in patients scheduled for renal surgery and to monitor the evolution of this gradient during the surgical procedure in these patients.

Methods

Patients

Thirty-five patients (20 men, 15 women; mean age 58 ± 18 yr) were included in the study after approval by the ethical committee of the Pitié-Salpêtrière Hospital, and informed consent was obtained. All had preoperative vital capacity and forced expiratory volume in 1 s within the normal range. All were free of cardiac disease; six were smokers. They were scheduled for renal or upper ureteral surgery to be performed via the lateral decubitus position.

Measurements

Blood gas analysis was performed on samples drawn from an indwelling radial artery catheter inserted under local anesthesia before induction of general anesthesia. Syringes were rinsed with sodium heparin to prevent coagulation. Blood gases were analyzed at 37°C, but all values were corrected automatically for body temperature according to the following formula (18):

$$PaCO_2\ (\text{mm Hg}) = PaCO_2\ (37°\text{C}) \times 10^{0.019(t° - 37)},$$

where t° is patient temperature. The P(a-ET)CO_2 difference was calculated with the temperature-corrected $PaCO_2$ value.

Expired gas tension was measured with a mass spectrometer. Calibration with known gas mixture was carried out periodically according to manufacturer specifications. Samples were drawn from a manifold located at the proximal end of the tracheal tube. The mean $PETCO_2$ value was determined by averaging the values obtained during the 15 s immediately before the collection of arterial blood. The P(a-ET)CO_2 was calculated as the difference between arterial and expired CO_2 partial pressures obtained simultaneously.

Arterial pressure was continuously measured from the radial artery catheter. Heart rate was obtained from the electrocardiogram monitored with the V_5 derivation. Body temperature was assessed with a Hewlett-Packard esophageal thermistor probe.

Procedure

In all subjects, anesthesia was induced with fentanyl (2 μg/kg) and thiopental (5 mg/kg). Tracheal intubation was facilitated with vecuronium (0.1 mg/kg). Patients were mechanically ventilated at a respiratory rate of 14 breaths/min with a tidal volume of 8 mL/kg. After induction of anesthesia, to facilitate the surgical procedure, the patients were positioned on their side and arched over a "kidney bridge" break in the table, with their hips flexed 30° vertically. Anesthesia was maintained with 60% nitrous oxide in oxygen, isoflurane, and fentanyl. Anesthetic agents were administered as required to avoid variations in mean arterial pressure >10% of stabilized values recorded after induction of anesthesia.

Measurements, including $PaCO_2$, $PETCO_2$, mean arterial pressure, heart rate, and temperature, were first performed in the supine position 10 min after induction of anesthesia, when hemodynamic status was stabilized. The patients were placed in the kidney position, and a second set of measurements were performed 5 min later. The same variables were then recorded at approximately 20-min intervals throughout the duration of surgery. Isoflurane and nitrous oxide were stopped after wound closure. The patients were replaced in the supine position, and a final set of measurements was obtained 5 min later.

Statistical Analysis

Data were analyzed with a two-way analysis of variance for repeated measurements. When *P* values were <0.05, the Student-Newman-Keuls multiple-range test was used to assess differences within groups. All results are reported as mean ± SD.

Results

Results of mean $PaCO_2$, $PETCO_2$, P(a-ET)CO_2, heart rate, temperature, and mean arterial pressure measurements are presented in Table 1. The duration of surgery ranged from 70 to 160 min (mean, 102 ± 41 min). Thus, only five measurements were obtained after the same duration of anesthesia in all patients (T1–T5); T6 and T7 represent values obtained just before and after the subjects were again placed in the supine position, respectively. Mean P(a-ET)CO_2, observed after induction of anesthesia (T1), was 4.8 ± 3.9 mm Hg, but great variations between patients were observed, because the values ranged from −0.7 to 15 mm Hg. With lateral decubitus positioning (T2),

Table 1. Hemodynamic Variables in 35 Patients Undergoing Renal Surgery

Measurement	Paco$_2$ (mm Hg)	Petco$_2$ (mm Hg)	P(a-et)co$_2$ (mm Hg)	HR (beats/min)	MAP (mm Hg)	Temp (°C)
T1 (10 min after induction)	36.6 ± 5.6	31.4 ± 4.8	4.8 ± 3.9	69.7 ± 15	84.4 ± 18.9	36.3 ± 0.4
T2 (5 min after DLP)	35.5 ± 4.3	27.7 ± 4.1^{a}	7.9 ± 3.5	64.4 ± 11	83.2 ± 11.4	35.9 ± 0.5
T3 (25 min after DLP)	34.9 ± 4.8	26.9 ± 3.7^{a}	8.2 ± 4.3^{a}	62.5 ± 13	85.2 ± 9.8	35.5 ± 0.5^{a}
T4 (45 min after DLP)	34.6 ± 4.8	26.2 ± 3.7^{a}	8.5 ± 4.1^{a}	64.5 ± 13	86.6 ± 13.5	35.2 ± 0.5^{a}
T5 (65 min after DLP)	34.1 ± 5.1	25.4 ± 4.1^{a}	8.8 ± 4.1^{a,b}	61.9 ± 11	86.5 ± 12.1	34.9 ± 0.5^{a}
T6 (after skin closure)	34.1 ± 5.2	25.4 ± 3.7^{a}	8.9 ± 4.4^{a,b}	61.5 ± 11	88.1 ± 13.1	34.8 ± 0.6^{a}
T7 (5 min after supine replacement)	34.6 ± 6.3	27.8 ± 5.5^{a,c}	6.9 ± 5^{a,c}	70.2 ± 16^{c}	99.2 ± 17.1^{c}	34.6 ± 0.6^{a}

DLP, decubitus lateral positioning; HR, heart rate; MAP, mean arterial pressure; Paco$_2$, arterial partial pressure of carbon dioxide; Petco$_2$, end-tidal partial pressure of carbon dioxide; P(a-et)co$_2$, arterial to end-tidal difference in partial pressure of carbon dioxide; Temp, temperature.

Data are mean ± sd.

[a] $P < 0.01$ vs T1.

[b] $P < 0.05$ vs T2.

[c] $P < 0.05$ vs T6.

P(a-et)co$_2$ increased to 7.9 ± 3.5 mm Hg ($P < 0.01$). The Petco$_2$ significantly decreased (from 31.4 ± 4.8 to 27.7 ± 4.1 mm Hg; $P < 0.01$), whereas Paco$_2$ did not significantly change. Further variations in alveolar-arterial gradient were observed with the maintenance of anesthesia, because a significant increase in mean P(a-et)co$_2$ was observed at T5 and T6 compared with T2 values (8.8 ± 4.1 and 8.9 ± 4.4 mm Hg, respectively; $P < 0.05$). Although the mean change in P(a-et)co$_2$ value was trivial but significant, large variations were observed between patients. The mean difference between gradient value at T6 and T2 was 1.18 ± 2.2 mm Hg (mean ± sd), and values ranged from −1.3 to 8.2 mm Hg. Furthermore great variations existed within patients. To illustrate this phenomenon, the difference between the greatest and the lowest gradient obtained between T2 and T6 was calculated patient by patient (Δgradient). The Δgradient ranged from 2.1 to 10.8 mm Hg (5.35 ± 2.65 mm Hg [mean ± sd]). When the patients were placed again in the supine position (T7), P(a-et)co$_2$ decreased (from 8.9 ± 4.4 to 6.9 ± 5.0 mm Hg; $P < 0.05$), whereas mean arterial pressure increased significantly (from 88.1 ± 13.1 to 99.2 ± 17.7 mm Hg; $P < 0.01$). Except for this last value, mean arterial pressure and heart rate remained constant throughout the study, but esophageal temperature dramatically decreased from 36.3 ± 0.4°C to 34.6 ± 0.6°C ($P < 0.001$).

Discussion

This study demonstrates that in anesthetized patients, the kidney position induces an increase in P(a-et)co$_2$. Further in this situation, the gradient may vary with prolongation of anesthesia despite the hemodynamic status remaining stable.

Several studies have been performed to evaluate the difference between arterial and end-tidal CO$_2$ measurements in adults or children under general anesthesia (4,8,14–17); values between 3 and 5.2 mm Hg have been reported. This variable was generally obtained with the patients lying supine. The mean P(a-et)co$_2$ of 4.8 mm Hg obtained after induction of anesthesia in this study compares reasonably well with the measurements of others. Consequences of other positions on P(a-et)co$_2$ have not been precisely evaluated. The enlargement in P(a-et)co$_2$ observed after positioning could be related to the alterations in ventilation/perfusion relationship that are known to occur in the lateral decubitus position. The anesthetized patient in the lateral decubitus position, with or without paralysis, has a nondependent lung that is well ventilated but poorly perfused, whereas the dependent lung is well perfused but poorly ventilated (11,19). This results in an increased degree of mismatching of ventilation and perfusion. As a result, the dead space increases, leading to an enlarged P(a-et)co$_2$. Lateral decubitus positioning has been shown to produce an increase in physiologic dead space between 0% and 13% (20–22); however, the kidney position used for renal surgery probably induced more extensive respiratory disturbances than the standard lateral decubitus position. Indeed, the patients were lying on their side but arched over a "bridge," with flexed hips. Thus, possible hemodynamic alterations could also be involved in the gradient variations observed with positioning. Mean arterial pressure was stabilized close to the supine values before the P(a-et)co$_2$ was measured. Right filling pressure or cardiac output, or both, which were not monitored, could have decreased. Because changes in either of these two variables can induce alterations in alveolar dead space (23,24), P(a-et)co$_2$ therefore could have been enlarged. Also, the bridge break in the table may result in compression of the base of the dependent lung and produce additional impairment in ventilation/perfusion relationships. Because of ethical considerations, cardiac output and filling pressures were not invasively monitored in this study. Thus, we were unable to determine whether hemodynamic alterations or changes in distribution of ventilation, or both, were responsible for gradient alterations.

Continued changes in P(a-ET)CO_2 were observed with prolongation of anesthesia. After the patients were positioned, the gradient progressively increased and became significantly greater 60 min later. Controversy persists with regard to stability of P(a-ET)CO_2 during anesthesia. Whitesell et al. (4) found that P(a-ET)CO_2 remained relatively constant with maintenance of anesthesia and could be applied as a correction to subsequent peak expired values to predict arterial CO_2. However, the delay between initial and subsequent measurements was not mentioned in their study and could have been insufficient to discover gradient variations. In contrast, Raemer et al. (15) observed important gradient variability between and within 15 patients during aortic or cardiac surgery. They could not identify which variable among arterial pressure, temperature, anesthesia duration, or minute ventilation was responsible for these variations. In our study, P(a-ET)CO_2 increased significantly during anesthesia. Although the mean increase was clinically trivial but statistically significant, there were some large variations in P(a-ET)CO_2 observed between and within patients. Many factors could be involved in this phenomenon. Despite arterial blood pressure stability, hemodynamic alterations probably occurred, because all patients presented some degree of hemorrhage during the time-course of the surgical procedure. Blood losses were compensated by plasma volume expansion or transfusion when necessary. Changes in cardiac output or filling pressures clearly could have occurred, resulting in modified alveolar dead space. This factor could contribute to both a progressive increase and to variations in P(a-ET)CO_2 within patients.

The progressive hypothermia observed in this study could have influenced P(a-ET)CO_2 values. Because gas solubility, pH, and pK of carbonic acid all change with temperature, there is a substantial physiologic decrease in PaCO_2 with hypothermia for a given CO_2 content of blood (25,26). To limit the influence of this variable on P(a-ET)CO_2 determination, arterial PaCO_2 values were measured at 37°C but corrected to patient temperatures before gradient calculation, because the use of the noncorrected PaCO_2 for P(a-ET)CO_2 calculation would have artificially increased the gradient value.

The alterations in P(a-ET)CO_2 could also be related to an impairment in gas exchange occurring with prolongation of anesthesia (27). Gunnarsson et al. (28) observed that patients under enflurane/nitrous oxide anesthesia exhibited significant increases in shunt and large increases in atelectasis between 30 and 90 min after induction of anesthesia. The influence of shunt on P(a-ET)CO_2 is probably trivial (29,30), but such alterations could influence the variations observed in this study.

The final set of measurements in our study was obtained when the patients were placed again in the supine position. Isoflurane was interrupted at this moment in all patients, which explains the increased arterial blood pressure, probably associated with increased cardiac output. These two phenomena, by reducing physiologic dead space (13,23), probably contributed to the decrease in P(a-ET)CO_2 observed at this time.

In conclusion, this study demonstrates that P(a-ET)CO_2 increases when patients are placed in the kidney position necessary for renal surgery. This phenomenon illustrates the respiratory and circulatory alterations likely to occur as a result of this position. Further, in this situation, the arterial to end-tidal CO_2 gradient may vary with prolongation of anesthesia. We do not believe it is valid to assume that a constant arterial to end-tidal CO_2 gradient exists when estimating PaCO_2 from PETCO_2 when the patient is in the lateral decubitus kidney position.

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Effect of Electroconvulsive Therapy on the Electrocardiogram and Echocardiogram

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Although electrocardiographic (ECG) ST segment depression is commonly induced by electroconvulsive therapy (ECT) for depression, it is unknown whether this reflects segmental myocardial ischemia, as is true under most circumstances, or a direct effect of central nervous system stimulation on cardiac repolarization in the absence of ischemic left ventricular regional wall motion abnormalities. We evaluated the association between ECG changes and left ventricular regional wall motion abnormalities detected by the echocardiograms performed before and after ECT in 11 patients. Immediately after ECT, three patients' ECGs revealed 1-mm downsloping or horizontal ST segment depression, one had a nonspecific ECG change (peaked T waves), and the ECG remained normal in seven. All patients had normal baseline echocardiograms. After ECT, at a time when the product of arterial blood pressure and heart rate was 100% above baseline values, five patients developed new left ventricular regional wall motion abnormalities that were confined to hypokinesia; no patient developed myocardial infarction or angina after ECT. Three patients with regional wall motion abnormalities developed ECG ST segment depression after ECT (sensitivity 60%), one had a nonspecific ECG change (peaked T waves), and the ECG of one patient remained normal. In conclusion, ECT may induce ECG changes with simultaneous regional wall motion abnormalities at a time when arterial blood pressure and heart rate are markedly elevated, findings that are highly suggestive of "demand" myocardial ischemia. In this small series, ECG or echocardiographic abnormalities did not predict clinical cardiac morbidity.

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Electroconvulsive therapy (ECT) has been advocated as the antidepressant therapy of choice in cardiac patients because of the cardiotoxic effects of psychotropic drugs (1); however, electrocardiographic (ECG) changes have been reported with ECT (2). Whether ECG changes observed with ECT or various neurologic diseases represent myocardial ischemia remains controversial, as do the mechanisms responsible for these changes (1,3,4). We used transthoracic echocardiograms immediately before and after initial ECT treatment with simultaneous ECG recording to determine whether ECG changes observed during ECT were accompanied by left ventricular regional wall motion abnormalities suggestive of segmental myocardial ischemia.

Methods

Twenty patients with mood disorders undergoing ECT were studied after giving informed written consent under a protocol approved by the Committee on Human Rights in Research of Cornell University Medical College. Pre-ECT or post-ECT (or both) echocardiograms in 9 patients were of insufficient quality to permit complete analysis, leaving 11 patients with complete studies. The patients (seven women, four men) ranged in age from 33 to 79 yr, with a mean of 54 yr. Five patients were receiving combinations of diuretics, angiotensin-converting enzyme inhibitors, and β-adrenoceptor or calcium-channel blocking drugs. Two patients had a history of myocardial infarction that clinically had been small in size. Eight of the 11 patients had at least one risk factor for atherosclerosis: hyperlipidema, hypertension, cigarette smoking, male gender, or diabetes mellitus. Eight patients had a family history of cardiac disease, five had at least one abnormality on their pre-ECT electrocardiogram (nonspecific repolariza-

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Table 1. Electrocardiographic and Echocardiographic Changes During Electroconvulsive Therapy in 11 Patients

ECG response to ECT	ECHO response to ECT: Normal wall motion	ECHO response to ECT: RWMA	No. of pts with coronary artery disease risk factors	No. of pts with family history of heart disease
Ischemia, ST depression (n = 3)		3	2	2
Nonspecific ECG change (n = 1)		1	1	1
Normal ECG response (n = 7)	6	1	5	5

ECG, electrocardiographic; ECHO, echocardiographic; ECT, electroconvulsive therapy; Pts, patients; RWMA, regional wall motion abnormalities.

tion abnormalities, n = 4; left ventricular hypertrophy, n = 1; or old myocardial infarction, n = 2).

Anesthesia administered consisted of intravenous thiopental (125–175 mg) and succinycholine (50–80 mg) and inhalation of 100% oxygen by a face mask. One patient received atracurium (25 mg IV) instead of succinycholine because of a history of poliomyelitis. Manual arterial blood pressure, lead II of the ECG, pulse oximetry, and echocardiographic monitors were used. Before anesthetic drugs were administered, baseline recordings of arterial blood pressure, heart rate, and lead II of the ECG were made. In addition, oxygen saturation (measured by pulse oximeter) and transthoracic two-dimensional long- and short-axis views of the left ventricle were recorded with an Acuson 128 echocardiograph. Bilateral ECT was delivered with use of standard placements and a MECTA SR device (5).

Beginning immediately after the induced seizure had ended, arterial pressure, heart rate, ECG waveform, and oxygen saturation were repeatedly measured at 1-min intervals and echocardiographic imaging every 2 min until all variables returned to baseline. Echocardiograms were interpreted in a blinded fashion and in random order by two experienced investigators unaware of the hemodynamic measurements and the course of the ECT treatment. The left ventricle was divided into 14 segments, and wall motion was graded as normal, hypokinetic, akinetic, or dyskinetic (6).

The association between regional wall motion abnormalities and ECG changes induced by ECT was tested by the χ^2 statistic with Yates' continuity correction, as were the associations between conventional cardiac risk factors and induced ECG and echocardiographic changes. Echocardiographic segmental regional wall motion abnormalities induced by ECT were used as the reference standard to calculate the sensitivity and positive predictive value of ECG changes by standard statistical definitions (7).

Results

In our 11 patients, 143 of 154 (93%) possible left ventricular (LV) wall regions were examined. Before ECT, all myocardial segments were normal. Immediately after ECT, five patients (45%) had hypokinesis of one or more contiguous myocardial segments involving the LV apex in three, the inferolateral wall in one, and the anteroseptal LV wall in one.

Immediately after ECT, diastolic and systolic arterial blood pressure and heart rate increased from baseline values in all 11 patients (from 129/82 ± 22/8 to 175/97 ± 20/11 mm Hg [mean ± SD], $P < 0.0001$ (systolic blood pressure)/0.0018 (diastolic pressure), and from 81 ± 7 to 127 ± 21 beats/min, $P < 0.0001$, respectively). Arterial pressure and heart rate had risen from baseline values of 132/79 ± 17/2 to 184/98 ± 15 mm Hg, $P < 0.001/0.041$, and 81 ± 8 to 118 ± 14 beats/min, $P < 0.018$, respectively, in the five patients who developed new segmental LV hypokinesia. Parallel changes in arterial blood pressure and heart rate from baseline to 2 min after ECT in the six patients who did not develop new regional wall motion abnormalities were from 127/84 ± 26/10 to 168/96 ± 21/7 mm Hg, $P < 0.002/0.028$, and from 80 ± 8 to 133 ± 25 beats/min, $P < 0.003$. All induced regional wall motion abnormalities occurred simultaneously, with substantial increases in heart rate and blood pressure. Oxygen saturation was maintained in the normal range (98%–99%).

Of the five patients in whom function of one or more initially normal LV segments deteriorated by one grade to hypokinesis, three developed new ECG changes suggestive of ischemia, with ≥1-mm horizontal or downsloping ST depression. In another of these five patients, the ECG revealed nonspecific repolarization abnormalities (peaked T wave). In seven patients, the ECG remained normal. All induced regional wall motion abnormalities and ECG changes occurred in the first 2–4 min after ECT, whereas arterial pressure and heart rate were near maximal values. The double product of heart rate and systolic pressure had increased by 103% over baseline at the time of these abnormalities. As Table 1 reveals, LV regional wall motion abnormalities were detected by echocardiography in all four patients in whom ECG abnormalities were induced by ECT but in only one of seven patients whose lead II recording remained normal ($\chi^2 = 4.88$, $P < 0.05$). Prevalence of conventional coronary risk factors and family history of heart disease was similar in patients with and without inducible ECG change or regional wall motion abnormality (χ^2 statistics = 0.003–0.88, all $P > 0.25$).

All ECGs and echocardiograms returned to baseline by the end of the study. No patient had a myocardial infarction. All patients' mood disorders improved with ECT.

Discussion

In the present study, we document the simultaneous induction of LV regional wall motion abnormalities and ECG changes during ECT. Regional wall motional abnormalities observed in our patients were limited to hypokinesia, with no akinesia or dyskinesia. Global LV hypokinesia may reflect altered loading conditions, and regional myocardial hypokinesia may be due to major ECG conduction defects rather than myocardial ischemia (8,9). The LV wall motion abnormalities induced by ECT in our patients were regional rather than global, occurred in regions corresponding to coronary artery distributions, and were not accompanied by major ECG conduction defects. There was a moderate and statistically significant concordance between ECG and echocardiographic changes during ECT in this patient population (Table 1). These characteristics of the induced wall motion abnormalities make it highly likely that they reflected segmental myocardial ischemia provoked by ECT.

Treadmill exercise testing is the test most commonly used to diagnose coronary artery disease (10). The stress of ECT on the heart, with marked increases in blood pressure and heart rate, has certain similarities to those imposed by treadmill exercise testing: both procedures may produce ST-T wave abnormalities and, as demonstrated in this study for ECT, regional wall motion abnormalities. However, treadmill testing uses aerobic exercise, whereas ECT induces central nervous system-mediated adrenergic hyperactivity and increased catecholamine release, as has been documented from our center in similar patients undergoing ECT by the same protocol (11). Testing by means of exercise and other stressors has shown that regional wall motion abnormalities are rare in truly normal individuals but are more common with early cardiomyopathy or angina with normal large coronary arteries ("syndrome x"). Overall, the positive predictive value of regional wall motion abnormalities seen at rest or developing during exercise echocardiography for detecting coronary artery disease on angiography is 80%–95% (10,12). Mild apical hypokinesia at peak exercise may be seen in patients with LV enlargement caused by severe valvular regurgitation, which was not present in any of our patients. Therefore, the occurrence in three of our patients who underwent ECT of both ST depression and regional wall motion abnormalities is highly suggestive of myocardial ischemia.

A limitation of our study was the difficulty in obtaining high-quality two-dimensional echocardiograms before and immediately after the acute stress of ECT. In contrast to the at least 80% success rate in obtaining fully adequate two-dimensional echocardiograms in middle-aged to elderly patients (13), the technical restrictions imposed by fasciculations due to succinylcholine and the rapidly changing study conditions after ECT reduced to 55% our yield of adequate studies. The excluded patients were similar in age, gender, risk factors, and incidence of ECG abnormalities to the patients with adequate echocardiograms. In addition, the sensitivity of our study may have been limited because only lead II of the ECG was used. One patient in the present study had peaked T waves after ECT treatment, with simultaneous onset of hypokinesis in the apical septal portion of the left ventricle, suggesting that this ECG change may have reflected myocardial ischemia.

In conclusion, our results document that ECG ST segment depression or other repolarization abnormalities provoked by the stress of ECT are associated with LV regional wall motion abnormalities. These appear to reflect "demand" myocardial ischemia, because they occur with marked blood pressure and heart rate increases at a time of documented intense adrenergic nervous system activation. Larger studies are needed to determine whether LV regional wall motion abnormalities provoked by ECT predict clinically significant complications of the procedure, and if so, to assess whether they can be prevented by medications such as short-acting β-blockers without exacerbating the underlying depression for which ECT is used.

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Ibuprofen Pretreatment Does Not Prevent Hemodynamic Instability After Cemented Arthroplasty in Dogs

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A bilateral cemented arthroplasty (BCA) in anesthetized mongrel dogs creates pulmonary fat and marrow embolism. A transient increase in plasma concentration of 6-keto prostaglandin $F_{1\alpha}$ and thromboxane B_2 has been associated with hemodynamic instability after BCA. We tested whether intravenous ibuprofen (20 mg/kg) could inhibit prostaglandin production, pulmonary hypertension, and decreased arterial blood pressure in this model. We found a decrease in cardiac output from 3.0 ± 0.5 to 2.2 ± 1.3 L/min (mean ± 1 SD) after BCA with a flow probe placed at thoracotomy around the ascending thoracic aorta. Systemic arterial blood pressure decreased from 140 ± 11 to 100 ± 15 mm Hg ($P < 0.0001$), and pulmonary artery pressure increased from 17.7 ± 3.3 to 37.1 ± 9.4 mm Hg ($P < 0.0001$). Similar hemodynamic changes were noted in 12 dogs without thoracotomy. Pretreatment with ibuprofen did not significantly attenuate the acute hemodynamic changes despite inhibiting prostaglandin generation. We conclude that decreased arterial blood pressure after BCA is associated with a decrease in cardiac output and that inhibition of prostaglandin production with ibuprofen does not prevent either pulmonary hypertension or systemic hypotension.

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Acute cardiopulmonary instability during cemented arthroplasty occurs at the time of cement and prosthesis insertion (1–3). Hemodynamic and gas-exchange abnormalities have been studied in patients (1–5) and in anesthetized animals (6) and are characterized by elevated pulmonary artery pressure (PAP) (6), reduced arterial blood pressure (BP) (1), and decreased systemic arterial oxygen tension (Pa_{O_2}) (3). Although hypotension is often transient, the cause of acute hemodynamic changes during cemented arthroplasty is important, because sudden cardiac arrest (5) and intraoperative deaths (7) have been reported. Intraoperative monitoring of patients during cemented arthroplasty with precordial Doppler (8) and transesophageal echocardiography (9) has detected pulmonary embolization of marrow contents.

Arachidonic acid metabolites are known to alter the vasoactive properties of both the pulmonary (10) and systemic (11) circulation. Infusion of fat and marrow emboli from donor animals causes an increased concentration of arachidonic acid metabolites detected in pulmonary lymph and blood (12,13). A simulated cemented arthroplasty procedure in anesthetized mongrel dogs has demonstrated an acute, transient increase in plasma thromboxane B_2 and 6-keto prostaglandin $F_{1\alpha}$ ($PGF_{1\alpha}$) accompanying fat embolism in vivo (14). Whether this prostanoid response to fat emboli contributes to hypertension by prostacyclin-induced vasodilation or to pulmonary hypertension by thromboxane A_2-induced vasoconstriction has not been studied. Patients having cemented arthroplasty procedures are often pretreated with ibuprofen, a nonsteroidal antiinflammatory drug that inhibits prostaglandin generation. This study evaluates whether ibuprofen could reduce pulmonary hypertension or systemic hypotension after cemented arthroplasty and reports acute changes in cardiac output associated with the decreased BP, pulmonary hypertension, and prostaglandin release in this model.

Methods

This study was approved by the local animal care committee, and all dogs were treated in accordance

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with the regulations of the Canadian Council on Animal Care. Twenty-one mongrel dogs weighing 28.5 ± 5.4 kg were anesthetized with intravenous pentobarbitone (30 mg/kg), followed by a continuous infusion ($0.5\ mg \cdot kg^{-1} \cdot h^{-1}$) of pentobarbitone, as required to maintain anesthesia and a stable hemodynamic state. The trachea was intubated in each animal. The lungs were mechanically ventilated with a nonrebreathing circuit using room air. Ventilation was adjusted before surgery to keep arterial blood Pco_2 at 35–40 mm Hg. Animals were paralyzed with pancuronium bromide (0.2 mg/kg), and lactated Ringer's solution was infused intravenously at a rate of $10\ mL \cdot kg^{-1} \cdot h^{-1}$ to maintain intravascular volume during the procedure.

Surgical exposure of both distal femoral condyles preceded physiologic measurements. In the control group of animals, prereaming measurements were made; then both femoral condyles were drilled and reamed retrogradely to a depth of 10 cm with successively larger reamers until a size 9 reamer was readily inserted. After reaming, all physiologic measurements were repeated (postreaming values). After the postreaming measurements were made, a bilateral cemented arthroplasty (BCA) was performed by injecting low-viscosity bone cement, mixed according to standard directions, into both intramedullary canals under manual pressure. Solid contoured metal prostheses were then hammered simultaneously into both intramedullary cavities to simulate prosthesis insertion. All measurements were repeated at predetermined intervals after BCA, as specified in the protocol.

Dogs were divided into two groups: the control group (*n* = 12) and the ibuprofen-pretreated group (*n* = 9). In both groups, the surgical technique and physiologic and pathological measurements used were standardized and are described later. The plasma assays and quantitative morphometric measurements were reported without previous knowledge of animal pretreatment.

In the control group (*n* = 12), a BCA procedure was performed without any prior drug administration. Control animals were treated with an infusion of saline solution (200 mL) over 20 min before BCA. In 6 of the 12 control animals, a thoracotomy was performed to place an ultrasonic flow probe around the ascending intrathoracic aorta. The flow probe measured pulsatile cardiac output. The other six animals in the control group had a BCA performed with an intact chest wall and intermittent measurement of cardiac output using the thermodilution technique.

The ibuprofen group (*n* = 9) received ibuprofen (20 mg/kg) diluted in 200 mL of saline solution administered intravenously before BCA. In three of the nine ibuprofen-pretreated animals, a thoracotomy was performed before BCA to place the ultrasonic flow probe around the ascending thoracic aorta to measure cardiac output. The animals with a thoracotomy were given ibuprofen after a set of predrug measurements and before reaming of the intramedullary canals. After the infusion of ibuprofen, a preream arterial blood sample was obtained to measure plasma thromboxane B_2 (TxB_2) and 6-keto $PGF_{1\alpha}$ concentrations. The intramedullary canals were then drilled and reamed, postreaming blood samples were taken, and a BCA was performed as described. The other six animals in the ibuprofen group were studied with an intact chest wall, and the ibuprofen was administered intravenously before baseline measurement to simulate preoperative ibuprofen therapy.

In all animals, the postreaming data serve as a baseline for comparison with subsequent measurements, because these measurements are taken after the blood loss of reaming and close in time to cement and prosthesis insertion, as previously described (6,14).

In all dogs, a 7F triple-lumen balloon-tipped pulmonary artery catheter was inserted into the left femoral vein and positioned in the pulmonary artery to measure PAP and right atrial pressure (RAP). The left carotid artery was cannulated with a pressure-tipped arterial catheter (Millar Instruments, Inc., Houston, Tex.), which was advanced into the ascending thoracic aorta to measure systemic arterial BP. All pressures were continuously recorded on a Gould ES 1000 recorder and are reported at 1, 5, and 15 min after BCA.

A left fifth interspace thoracotomy was performed in nine dogs: six control dogs and three dogs pretreated with ibuprofen. After incising the pericardium, a 7F catheter was sutured directly into the left atrium to monitor left atrial pressure (LAP) continuously. A T_{201} ultrasonic blood flowmeter (Transonic Systems, Inc., Ithaca, N.Y.) was placed around the ascending thoracic aorta to continuously measure pulsatile cardiac output (aortic flow).

In dogs without a thoracotomy (six control and six pretreated with ibuprofen), a Cordis 7F pigtail catheter was inserted through the carotid artery into the left atrium via the left ventricle. This catheter was used to measure LAP directly. Cardiac output was measured using thermodilution technique in triplicate at each measurement period. The mean of three determinations was used as representative of cardiac output at each measurement time. Because the thermodilution technique is most accurate if a stable hemodynamic state exists, we did not measure cardiac output at the 1-min time period in dogs without a thoracotomy.

We sampled arterial blood from the descending thoracic aorta for measurement of the plasma concentration of arachidonic acid metabolites, 6-keto $PGF_{1\alpha}$ and TxB_2. Blood samples were taken for plasma assays at the following time intervals: before reaming, immediately after reaming, 1, 5, and 15 min after BCA.

Each blood sample (9 mL) was collected in a plastic syringe containing 1 mL of an indomethacin/anticoagulant (ethylenediaminetetraacetate [EDTA]) solution. This solution was prepared by diluting (1:20) the stock indomethacin (0.04 M indomethacin in ethanol) in an EDTA anticoagulant. The anticoagulant was prepared by dissolving 2 g of disodium EDTA and 0.8 g of sodium chloride in 100 mL of water. The pH was adjusted to 7.4 by adding sodium hydroxide. Indomethacin was added to inhibit any further production of arachidonic acid metabolites in vitro after sampling. Each blood sample was then mixed and immediately transferred to a plastic centrifuge tube, centrifuged, and the plasma collected. The plasma was then transferred to polypropylene tubes and frozen immediately at −20°C for storage.

The plasma concentrations of the stable metabolite of thromboxane A_2, TxB_2, and 6-keto $PGF_{1\alpha}$, the stable metabolite of prostacyclin, were determined by radioimmunoassay. The radioimmunoassay kits used labeled I^{125} tracers from Dupont Canada. All plasma samples and standards were analyzed in duplicate. Samples were measured, and standard curves were constructed. The gamma counter was LKB model 1277 (Wallac Oy, Turku, Finland). The intra- and interassay coefficients of variation were, respectively, 7.6% and 6.1% for TxB_2 measurements and 4.0% and 9.4% for 6-keto $PGF_{1\alpha}$. Results from duplicate samples showed good reproducibility (<10% variation). The lowest level of detection with these methods was 0.005 ng/mL for TxB_2 and 0.01 ng/mL for 6-keto $PGF_{1\alpha}$.

After completing each study, the 12 anesthetized dogs without a thoracotomy (6 control and 6 ibuprofen pretreated) were killed by injecting pentobarbital (200 mg) and KCl through the left atrial cannula. A postmortem thoracotomy was performed and the pulmonary vessels ligated. The lungs were removed en bloc and fixed in inflation with 10% buffered formalin at a pressure of 25 cm of fixative. After fixation for 72 h, the lungs were sectioned in the midsagittal plane, and three stratified random blocks of known size were taken from the midsagittal slice of each lung. These samples were postfixed in Fleming's solution for 72 h, washed in running water for 24 h, processed for histologic examination in the usual manner, and cut at 5-μm thickness.

The sections were then evaluated with a TV-based image analysis system (BQ Meg IV, R and M Biometrics, Nashville, Tenn.). This system has a Leitz Dialux 22 microscope attached to a Sony CCD video camera connected to an IBM AT compatible microcomputer. For each animal, 12 stratified random fields (each 1 mm^2) from the six lung samples were examined for a total area of 72 mm^2 per animal. The measurements were made at a final optical magnification of 245×. The gray scale image was converted to a binary (black-and-white) image by manual selection of the threshold value that best delineated the emboli from background. The area and diameter of each embolus was calculated. The ratio of area occupied by fat emboli to total area of lung examined is equivalent to the volume proportion of lung tissue occupied by fat (Delesse's principle). The number of fat emboli and volume proportion of lung tissue occupied by fat after BCA in each group could then be compared.

Data are reported as mean values ± 1 SD. Data were analyzed with the SAS (Statistical Analysis Software) statistical software package. We used the SAS general linear model repeated measures analysis of variance procedure to analyze data from sequential measurements. When a significant F ratio was present ($P < 0.05$), multiple comparisons within groups between baseline (postream) and other measurements were made using unadjusted pairwise comparisons, as printed out by LSMEANS comparison procedure, with adjustment made on the probability of rejection with Bonferroni's correction (15). If there was significant group and time interaction, multiple comparisons with baseline values within groups were determined with Dunnett's test.

Results

There was no significant difference in the mean weight of dogs included in the control (27.8 ± 5.5 kg) and the ibuprofen-pretreated (26.4 ± 5.9 kg) groups. No difference was found between the baseline hemodynamic measurements of control and ibuprofen-treated dogs.

Control Group: Hemodynamic and Gas-Exchange Data

In the control group with a thoracotomy ($n = 6$), a significant decrease in mean BP was noted from 140 ± 11 mm Hg before BCA to a minimal value of 100 ± 15 mm Hg within 1 min of BCA. The aortic flow decreased in every control dog studied. In the control group, the aortic flow decreased ($P < 0.0002$) from a mean value of 3.0 ± 0.5 L/min after reaming to 2.2 ± 1.3 L/min within 2 min of BCA, returning to 2.7 ± 1.4 L/min by 5 min after BCA. This decrease in flow occurred simultaneously with an increase in PAP. Mean PAP increased significantly ($P < 0.0001$) from 17.7 ± 3.3 to 37.1 ± 9.4 mm Hg within 1 min of BCA

Table 1. Hemodynamic Data (mean ± SD) Before and After Bilateral Cemented Arthroplasty in 12 Dogs With Intact Chest Walls

	Preream	Postream	1–3 min after BCA	5 min after BCA
BP (mm Hg)				
Control	158 ± 7	148 ± 5	120 ± 19[a]	142 ± 17
Ibuprofen	161 ± 7	145 ± 14	131 ± 17[a]	143 ± 15
PAP (mm Hg)				
Control	14.1 ± 2.6	13.8 ± 3.4	32.2 ± 12.5[a]	30.1 ± 10.2[a]
Ibuprofen	15.1 ± 3.4	14.2 ± 3.6	32.3 ± 6.9[a]	30.8 ± 4.6[a]
RAP (mm Hg)				
Control	3.2 ± 1	3.2 ± 1.2	4 ± 1.5	4.1 ± 1.1
Ibuprofen	1.8 ± 4.1	1.8 ± 3.3	1.5 ± 3.5	1.8 ± 4.5
LAP (mm Hg)				
Control	2 ± 6.8	3.8 ± 2.7	4.6 ± 4.1	4.7 ± 3.7
Ibuprofen	8.5 ± 3.5	7.3 ± 5.1	7.3 ± 4.6	6.4 ± 4.3
Q (L/min)				
Control	3.7 ± 0.9	3.2 ± 0.9		2.8 ± 0.6
Ibuprofen	4.4 ± 1	3.5 ± 0.8		3.2 ± 1
Pa_{O_2} (mm Hg)				
Control	104.1 ± 4.7	106.1 ± 4.5	95.6 ± 4.1[a]	87.6 ± 5.9[a,b]
Ibuprofen	105.9 ± 3.6	107.9 ± 2.1	99.7 ± 6.8[a]	97.2 ± 3.6[a,b]

BCA, bilateral cemented arthroplasty; BP, arterial blood pressure; Control, control group (*n* = 6); Ibuprofen, ibuprofen (20 mg/kg)-pretreated group (*n* = 6); PAP, pulmonary artery pressure; RAP, right atrial pressure; LAP, left atrial pressure; Q, thermodilution cardiac output; Pa_{O_2}, arterial P_{O_2}.

[a] Significant difference from baseline (postream) values.

[b] Significant difference between groups at this measurement time.

and remained elevated at 28.0 ± 4.3 mm Hg at the 5-min measurement. Mean PAP remained elevated ($P < 0.0001$) throughout the 15-min study (26.7 ± 2.9 mm Hg). No changes in RAP or LAP were noted during the 15-min study period in this group.

In the six control dogs without a thoracotomy, the BP decreased significantly from a postream value of 148 ± 5 mm Hg to a minimal value of 120 ± 19 mm Hg approximately 1 min after BCA (Table 1). The BP returned to baseline levels within 5 min of BCA. The PAP increased ($P < 0.005$) after BCA, and no change in RAP or LAP was noted. Cardiac output was measured at the 5-min measurement period and was not significantly different from baseline value at this time, whereas PAP remained elevated above baseline value. The Pa_{O_2} decreased from baseline to both the 1- and 5-min measurements. No differences between pre- and postreaming (baseline) measurements were noted.

Ibuprofen Group: Hemodynamic and Gas-Exchange Data

No difference was noted in baseline measurements between the ibuprofen-pretreated dogs with a thoracotomy ($n = 3$) and the control group. Mean BP decreased from 168, 135, and 152 mm Hg before BCA to 138, 112, and 126 mm Hg, respectively, within 1 min of BCA in the three ibuprofen dogs. No change in LAP or RAP was found. The PAP increased within 1 min of BCA from 17.7, 11.3, and 16.0 mm Hg to 35.7, 36.3, and 27.3 mm Hg, respectively. Aortic flow decreased from 2.2, 2.9, and 3.2 L/min to 1.6, 2.3, and 2.8 L/min, respectively, after BCA. Cardiac output and BP returned to baseline levels within 5 min despite a persistent increase in PAP.

In ibuprofen-pretreated animals with an intact chest wall, no difference between the prereaming and postreaming measurements was noted (Table 1). The BP decreased from 145 ± 14 to 131 ± 17 mm Hg within 3 min of BCA, returning to baseline value by the 5-min measurement. The PAP increased from 14.2 ± 3.6 to 32.3 ± 6.9 mm Hg within 1 min of BCA. No change in RAP or LAP was noted. The cardiac output measured by thermal dilution technique at the 5-min measurement was not significantly different from the baseline value. No difference between groups was noted in the change of BP, PAP, or cardiac output from baseline. The Pa_{O_2} at the 1- and 5-min measurements was significantly different from the baseline value. The 1-min Pa_{O_2} was not significantly less than that noted in the control group at the same period; however, the 5-min Pa_{O_2} (97.2 ± 3.6 mm Hg) was significantly higher than that noted in control animals (87.6 ± 5.9 mm Hg).

Prostaglandin Assays

In the control group of animals that had a thoracotomy ($n = 6$), the plasma 6-keto $PGF_{1\alpha}$ concentra-

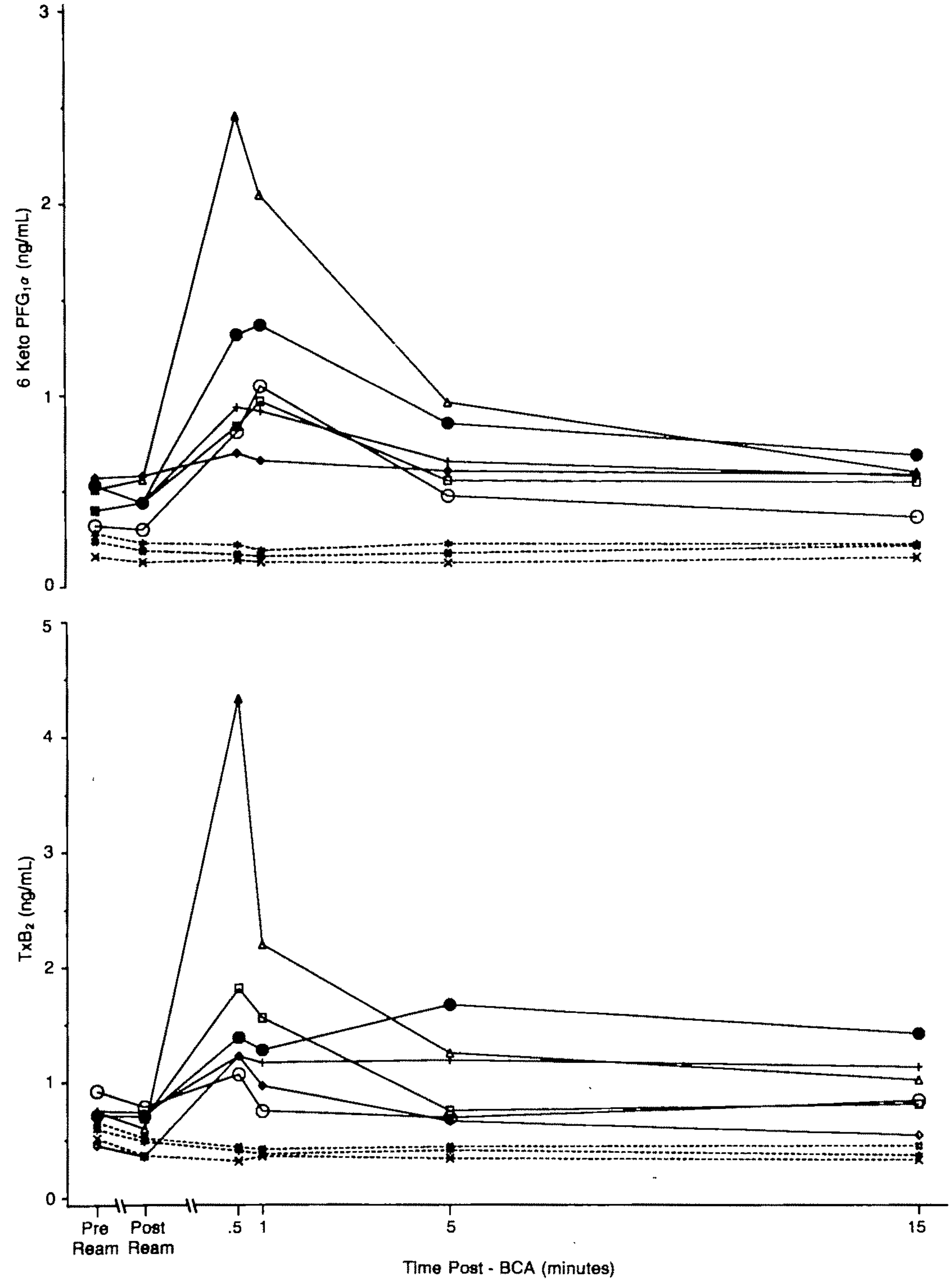

Figure 1. Measured arterial plasma thromboxane B_2 (TxB_2) and 6-keto prostaglandin $F_{1\alpha}$ (6-keto $PGF_{1\alpha}$) concentrations in control ($n = 6$) dogs (*solid lines*) with thoracotomy after bilateral cemented arthroplasty (Post-BCA) and in three ibuprofen (20 mg/kg) pretreated animals (*dashed lines*).

tion increased significantly above baseline (0.46 ± 0.10 ng/mL) to the 30-s and 1-min measurements (1.18 ± 0.66 and 1.17 ± 0.49 ng/mL, respectively) (Figure 1). The plasma TxB_2 concentration increased significantly from baseline (0.64 ± 0.15 ng/mL) in the same group to a mean value of 1.84 ± 1.25 and 1.31 ± 0.51 ng/mL at 30 and 60 s after BCA, respectively.

No increase from baseline plasma TxB_2 or 6-keto

Table 2. Arterial Plasma Concentration (mean ± SD) of Thromboxane B_2 and 6-Keto Prostaglandin $F_{1\alpha}$ in 12 Dogs With an Intact Chest Wall at Each Measurement Time

	Postreaming	1 min after BCA	5 min after BCA	15 min after BCA
TxB_2				
Control	0.80 ± 0.65	1.23 ± 0.69[a]	1.02 ± 0.48	0.97 ± 0.42
Ibuprofen	0.35 ± 0.08[b]	0.28 ± 0.06[b]	0.28 ± 0.03[b]	0.28 ± 0.04[b]
6-Keto $PGF_{1\alpha}$				
Control	0.29 ± 0.11	1.19 ± 0.37[a]	0.77 ± 0.33[a]	0.42 ± 0.17
Ibuprofen	0.09 ± 0.03[b]	0.07 ± 0.03[b]	0.07 ± 0.03[b]	0.07 ± 0.03[b]

BCA, bilateral cemented arthroplasty; TxB_2, thromboxane B_2; 6-keto $PGF_{1\alpha}$, 6-keto prostaglandin $F_{1\alpha}$; Control, control group ($n = 6$); Ibuprofen, ibuprofen (20 mg/kg)-pretreatment group ($n = 6$).

[a] Significant increase from the postreaming (baseline) values.

[b] Significant difference from the same measurement time in the control group.

$PGF_{1\alpha}$ was found at any measurement period in the ibuprofen-pretreated dogs ($n = 3$).

In the control group of animals with an intact chest wall (no thoracotomy), a significant increase in plasma TxB_2 and 6-keto $PGF_{1\alpha}$ was found within 5 min of BCA (Table 2). In ibuprofen-pretreated dogs without a thoracotomy, the arterial plasma concentration of TxB_2 and 6-keto $PGF_{1\alpha}$ was significantly lower (Table 2) than in the control group. The ibuprofen-pretreated dogs had no increase in plasma TxB_2 after BCA, whereas the control group had a significant increase at the 1-min measurement. Similarly, in the ibuprofen group, no increase from baseline plasma 6-keto $PGF_{1\alpha}$ concentration was found, whereas plasma 6-keto $PGF_{1\alpha}$ concentration in the control group increased at the 1-min measurement.

Quantitative Estimate of Fat Embolus

Quantitative morphometry of postmortem lung tissue compared the amount of fat embolized to the lung in the two groups of dogs without a previous thoracotomy. The volume proportion of lung occluded by fat was not significantly different between the control group (1.27% ± 0.29%) and the ibuprofen group (1.10% ± 0.25%). The size of vessels occluded by fat ranged from 7.0 to 14.3 μm, and no significant difference was found between groups in the size distribution of pulmonary vessels occluded by fat.

Discussion

This animal model (6) simulates hemodynamic changes during massive fat embolism, which is an infrequent clinical complication during cemented arthroplasty. To create this degree of fat and marrow embolism, we maximized the embolic load by performing bilateral, simultaneous arthroplasties using high-pressure prostheses with no lavage of the marrow cavity before BCA. This procedure creates reproducible, transient hemodynamic changes and pathological evidence of fat embolism similar to the fatal, massive embolism that has been reported in patients (5,7).

Fat and marrow embolism after BCA causes acute pulmonary hypertension (5) associated with transient hypotension (6). This study verifies our previous report (14) of a transient increase in plasma TxB_2 and 6-keto $PGF_{1\alpha}$ concentrations after BCA in this model (Figure 1, Table 2). Inhibiting the production of both vasoactive prostanoids by pretreating with ibuprofen (thus inhibiting the cyclooxygenase enzyme) was of interest for two reasons. First, many patients undergoing cemented arthroplasty receive long-term treatment with nonsteroidal antiinflammatory drugs; second, cyclooxygenase enzyme inhibition has attenuated pulmonary hypertension when particulate fat and marrow were infused from donor animals into recipients to create acute lung injury (13). In our study, significant pulmonary hypertension followed BCA in both groups, and ibuprofen was ineffective in reducing the PAP increase (Table 1). Similar results have been reported after air embolism (16).

If prostacyclin-induced vasodilation is a primary cause of systemic hypotension, ibuprofen pretreatment might reduce the decrease in BP. This study demonstrated that ibuprofen administered before BCA did not prevent the transient decrease in BP induced by cement and prosthesis insertion despite suppression of the prostanoid response (Table 2, Figure 1).

Quantitative morphometry of the lung demonstrated an equivalent "embolic load" in the control and ibuprofen-pretreated groups. The failure of ibuprofen to alter the hemodynamic changes was not due to a difference in either the number of emboli or the proportion of lung vasculature occluded by fat. Quantitative morphometry was not performed in dogs having a thoracotomy, because altered lung perfusion might change the intrapulmonary distribution of emboli and invalidate the quantitative estimate of embolic load. The use of a quantitative technique for comparison of embolic load is an important asset of the model, because clinical studies cannot quantify or compare the degree of fat embolism between groups. Clinical echocardiographic detection of embolic material (8,9) cannot precisely quantify the amount of fat in the lung. The surgical technique was standardized for all dogs; however, we must assume that the number of emboli in dogs with a thoracotomy was comparable to that in dogs with an intact chest wall, because similar hemodynamic and prostanoid changes were noted in both groups.

Because a stable hemodynamic state for reliable measurement of cardiac output often is not present in clinical practice, the cause of transient hypotension immediately after cement and prosthesis insertion has been difficult to evaluate (2). Pulmonary hypertension with fat embolism is a rare clinical event, making a detailed study of this problem difficult. Our data demonstrate that the decreased BP after BCA is associated with a transient decrease in cardiac output and that this reduced cardiac output is independent of prostaglandin production.

In these mongrel dogs, the decrease in cardiac output was transient, whereas significant pulmonary hypertension persisted. Because many patients having cemented arthroplasty are elderly and have cardiopulmonary disease, they may have less reserve to cope with a sudden increase in PAP and decrease in cardiac output. Moreover, the decrease in BP could be more protracted and more severe in high-risk patients than in these healthy dogs. The failure of ibuprofen to attenuate the decrease in BP in this model suggests that the transient increase in prostacyclin does not cause hypotension by vasodilation alone. Both LAP and RAP remained constant, suggesting that the acute reduction in aortic flow was not secondary to acute intravascular volume depletion.

Possible causes of hemodynamic instability after BCA include methylmethacrylate-induced vasodilation (17,18), reflex changes (19), generation of tissue thromboplastic products (1), prostaglandin release (14), and myocardial depression (20), as well as the mechanical effects of emboli. Our study does not address the specific role of cement in producing the hemodynamic changes after BCA, but it does document that a transient decrease in cardiac output accompanies the decreased BP and pulmonary hypertension. The failure of ibuprofen to alter this hemodynamic response suggests that either prostaglandin production is not a primary cause of hypotension or that the physiologic effects of the vasoconstrictor (thromboxane A_2) balance the effect of prostacyclin after cement and prosthesis insertion. This study also suggests that the pulmonary hypertension after fat embolism is not caused by thromboxane release. The decrease in cardiac output may result primarily from increased right ventricular afterload caused by elevated pulmonary vascular resistance. Alternatively, multiple factors, such as myocardial depression and systemic vasodilation, could interact with acute right ventricular dysfunction to cause the decrease in cardiac output.

In conclusion, this study suggests that pretreatment with ibuprofen before BCA does not reduce acute pulmonary hypertension or transient systemic hypotension associated with fat and marrow embolism during cemented arthroplasty. Also, these data show that the sustained pulmonary hypertension and transient decrease in BP are associated with a transiently reduced cardiac output.

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Fentanyl Does Not Alter the "Sleep" Plasma Concentration of Thiopental

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Thiopental and fentanyl are commonly combined for induction of anesthesia. The effect of an analgesic concentration of fentanyl on the plasma concentration of thiopental to induce sleep was studied in 46 unpremedicated patients. As a measure of drug effect, sleep (the lack of response to open eyes to a verbal command) was used. Forty-six patients were randomized to receive thiopental infused to one of several predetermined plasma concentrations. Twenty-two of these patients also received a fentanyl infusion to a desired analgesic concentration of 1 ng/mL. Thiopental and fentanyl were infused by means of a pharmacokinetic model-driven infusion device (computer-assisted continuous infusion, CACI). Venous blood samples were taken from the contralateral antecubital fossa at 5 and 10 min after the start of the infusion. At 10 min, the patients' names were firmly spoken, and they were instructed to open their eyes. If they did not respond to this command, they were considered to be asleep. Only patients in whom the 5- and 10-min measured plasma concentrations of thiopental and fentanyl, respectively, were within ±30% of each other were used for the determination of the Cp_{50}(asleep), the plasma concentration at which 50% of the patients were asleep. The Cp_{50}(asleep) with and without fentanyl was calculated by logistic regression. The Cp_{50}(asleep) for patients in whom concentrations were maintained within ±30% for thiopental alone ($n = 17$) was 7.32 μg/mL (95% confidence interval, 5.53–10.95); for thiopental in the presence of fentanyl ($n = 18$ with a measured fentanyl concentration of 1.27 ± 0.5 ng/mL), this was 7.22 μg/mL (95% confidence interval, 4.83–10.15). There was no interaction between fentanyl (up to a concentration of 2.1 ng/mL) and the Cp_{50}(asleep) for thiopental. We conclude that fentanyl, at an analgesic concentration, has no effect on the hypnotic concentration of thiopental.

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Thiopental has been administered intravenously to induce anesthesia for >40 yr. During this time there have been many studies that have considered the amount of thiopental necessary for induction of anesthesia, the amount of thiopental necessary to abolish verbal counting, and the amount of thiopental necessary to abolish the response to surgical stimulation (1–5). These studies have used conventional dosing methodology, and their results may be misleading because of the influence of both pharmacokinetics and pharmacodynamics in characterizing the relationship among dose, plasma concentration, effect site concentration, and the response that is being observed (6). A single bolus dose results in a continuously changing plasma concentration and pharmacodynamic effect that are not linearly related; rather, they demonstrate hysteresis. Thus, when two drugs are administered as a bolus dose, the interaction observed is only applicable to the given dose of each drug and the time interval between drug administration and assessment of the pharmacodynamic response. Methods that ensure equilibration between the plasma concentration of a drug and the effect compartment accurately define the concentration-response relationship and therefore provide a time- and dose-independant evaluation of the pharmacodynamic interaction that may occur when two drugs are administered together. Fentanyl is commonly combined with thiopental for the induction of anesthesia. It is therefore important to establish the interaction of these two drugs in producing sleep (hypnosis). The purpose of this study was (a) to establish the concentration of thiopental necessary for hypnosis in 50% of patients [Cp_{50}(asleep)], and (b) to determine

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whether an analgesic concentration of fentanyl alters the Cp_{50}(asleep) of thiopental.

Methods

After institutional review board approval of the protocol, written, informed consent was obtained from 46 patients. Patients <18 yr and those with a history of alcohol or drug abuse or presently receiving any hypnotic or opiate analgesics were excluded.

Patients were not premedicated before the study. When these unpremedicated patients arrived in the operating room, an intravenous catheter was inserted for fluid and drug administration. A second catheter was inserted in the contralateral antecubital vein to obtain blood samples for measurement of subsequent thiopental and fentanyl concentrations. Thiopental and fentanyl were infused with a pharmacokinetic model-driven drug-delivery device (computer-assisted continuous infusion, CACI) (7). This device uses pharmacokinetic simulations and infusion algorithms to calculate the infusion rate (every 9 s) required to immediately obtain and then maintain the set plasma concentration. The device then delivers this infusion rate by an infusion pump to the patient (8). The microcomputer was programmed with thiopental pharmacokinetic variables previously reported by Ghoneim and Van Hamme (9) and fentanyl kinetic variables reported by McClain and Hug (10).

Forty-six patients were randomly allocated to receive thiopental at a predicted plasma concentration of 5, 7.5, 10, 15, 20, or 25 μg/mL. In 22 patients, fentanyl was infused to a predicted (set) plasma concentration of 1 ng/mL. At 5 and 10 min after the initiation of the infusion, blood samples were drawn for subsequent measurement of drug concentration. At 5 and 10 min, patients' names were firmly spoken, and they were instructed to open their eyes. If patients did not respond to this command at 10 min, they were considered to be asleep.

The blood samples were immediately placed on ice, after which the plasma was separated and frozen at −70°C until assayed. The plasma concentration of fentanyl was measured by radioimmunoassay with fentanyl antisera and tritiated fentanyl (Fentanyl Radioimmunoassay kit, Janssen Biochemica, Belgium) (11). The lower limit of detection of the assay was 0.2 ng/mL. Total serum thiopental concentrations were measured with a high-performance liquid chromatographic assay sensitive to 100 ng/mL (12). The coefficient of variation of both assays was <10% over the concentration range measured. All assays were performed in duplicate. If the two measurements differed by >10%, the sample was reassayed.

To ensure that a stable plasma concentration of thiopental and fentanyl was maintained during the infusion, the 5- and 10-min samples were compared. Only pairs in which the 5-min sample was within ±30% of the 10-min sample were utilized for the calculation of Cp_{50}(asleep). Each 10-min sample was characterized as asleep/not asleep, and this plasma concentration was used in the determination of the concentration at which 50% of the patients were asleep Cp_{50}(asleep), which was calculated by logistic regression. The fit of the data to the model was accomplished with an iterative maximal likelihood technique (13). A Cp_{90}(asleep) (i.e., the plasma concentration at which 90% of the patients did not respond to a verbal stimulus) was similarly derived. The interaction of increasing fentanyl concentration on the Cp_{50}(asleep) of thiopental was also evaluated with a similar iterative maximal likelihood technique. The effect of age on the Cp_{50}(asleep) was also determined with age as a covariate in the model. For comparisons between groups, an unpaired Student's *t*-test was used. A P value <0.05 was considered significant. Fentanyl concentrations and demographic values were averaged, and the mean ±SD is reported.

Results

Forty-six patients completed the study. Of these, 24 received thiopental only, and 22 received thiopental plus fentanyl. The average age for patients receiving thiopental only was 32 ± 14 yr (range 18–71). The average age of patients receiving thiopental plus fentanyl was 41 ± 14 yr (range 18–64) ($P > 0.05$). The gender distribution in the two groups was 9 women and 15 men in the thiopental-only group and 8 women and 14 men in the combined thiopental-fentanyl group.

In 17 of 24 patients in the thiopental-only group, the 10-min sample was within ±30% of the 5-min sample. In the combined thiopental-fentanyl group, 18 of 22 patients had both fentanyl and thiopental 10-min concentrations within ±30% of the 5-min sample. The 5- and 10-min concentrations for all patients are illustrated in Figure 1. Only one patient was assessed as asleep at 5 min and awake at 10 min. In this patient, the thiopental concentration at 5 min was 7.6 μg/mL and at 10 min 5.5 μg/mL. Two patients were awake at 5 min (thiopental plasma concentration 11 and 7.5 μg/mL) and asleep at 10 min (thiopental plasma concentration 11.7 and 6.3 μg/mL).

In those patients meeting the criteria of maintaining the 5- and 10-min measured concentrations of thiopental and fentanyl within ±30%, the average measured concentration of fentanyl at 10 min was 1.27 ± 0.5 ng/mL (range 0.35–2.1). Because the fentanyl concentration was not exactly the same in each

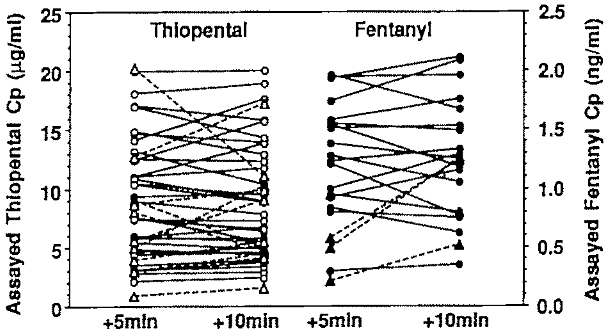

Figure 1. Measured plasma concentrations (Cp) of thiopental and fentanyl in 46 patients at 5 and 10 min after the start of an infusion intended to maintain a constant concentration of either or both drugs. *Solid line,* patients (n = 24) in whom the 5- and 10-min samples were within ±30%; *dashed line,* patients (n = 22) in whom the 5- and 10-min samples were not within ±30% and were subsequently excluded from the calculation of the Cp_{50}(asleep).

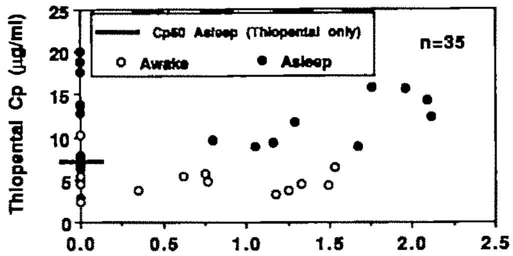

Figure 2. Thiopental and fentanyl plasma concentrations (Cp) at which patients (n = 35) were either awake or asleep (lack of response to open eyes to a verbal command) are plotted. No interaction between increasing fentanyl concentration (0–2.1 ng/mL) and the thiopental Cp_{50}(asleep) could be demonstrated.

patient, the thiopental versus fentanyl concentrations for patients asleep/not asleep are presented in Figure 2. Figure 2 demonstrates the lack of effect of increasing fentanyl concentration on the thiopental Cp_{50}(asleep). Analysis of the data showed no interaction of increasing fentanyl concentration (over the range 0–2.1 ng) with the thiopental Cp_{50}(asleep) ($P > 0.5$). Thus, all patients receiving fentanyl were grouped together. The Cp_{50}(asleep) (Table 1) for thiopental alone was 7.32 µg/mL (95% confidence interval, 5.53–10.95) (Figure 3), and in patients receiving fentanyl, the Cp_{50}(asleep) for thiopental was 7.22 µg/mL (95% confidence interval, 4.83–10.16) (Figure 4). There was no difference between the thiopental alone Cp_{50}(asleep) and the combined thiopental-fentanyl Cp_{50}(asleep) ($P > 0.5$). Because the Cp_{50}(asleep) for thiopental was not altered by the presence of fentanyl, all patients in whom the plasma concentration was maintained within ±30% were combined, and a Cp_{50}(asleep) value for this population was calculated (Table 1). For the 35 patients (age range 18–71 yr) included in the analysis of the Cp_{50}(asleep), age was neither a significant predictor of response nor a significant cofactor within the model ($P > 0.5$).

Table 1. Cp_{50}(asleep) and Cp_{90}(asleep) Values in 46 Patients

	Thiopental Cp_{50}(asleep) (µg/mL [95% CI])	Thiopental Cp_{90}(asleep) (µg/mL [95% CI])
Thiopental only, 5- and 10-min samples within ±30% (n = 17)	7.3 (5.5–10.9)	9.9 (7.8–27.1)
Thiopental plus fentanyl, 5- and 10-min samples within ±30% (n = 18)	7.2 (4.8–10.2)	9.8 (7.6–22.5)
Thiopental and thiopental plus fentanyl, 5- and 10-min samples within ±30% (n = 35)	7.3 (5.8–9.4)	9.8 (8.1–22.6)

Cp_{50}(asleep), thiopental concentration at which 50% of the patients were asleep, as assessed by a lack of response to their name being called; Cp_{90}(asleep), thiopental concentration at which 90% of patients were similarly assessed as asleep; CI, confidence interval.

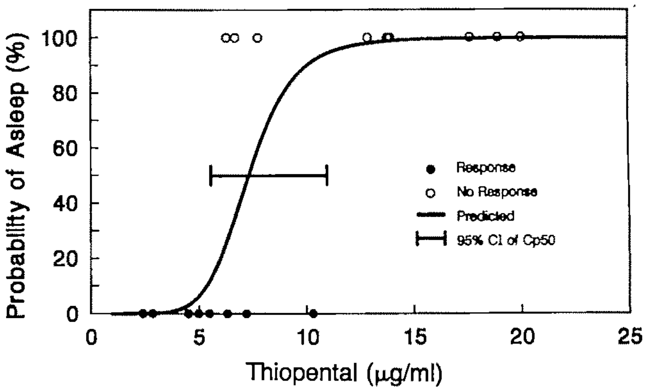

Figure 3. Thiopental plasma concentration at which patients (n = 17) were either awake or asleep (lack of response to open eyes to a verbal command) after 10 min of an infusion of thiopental maintained at a constant concentration. The thiopental plasma concentration at which there is a 50% probability of a patient not responding to a verbal command (Cp50) is 7.35 µg/mL (95% confidence interval, 5.5–10.9).

Discussion

This study established the hypnotic concentration of thiopental as 7.3 µg/mL (95% confidence interval, 5.5–10.9), and this was unaltered by an analgesic concentration of fentanyl up to 2.1 ng/mL.

Anesthesia commonly requires the administration of more than a single drug. For the inhaled anes-

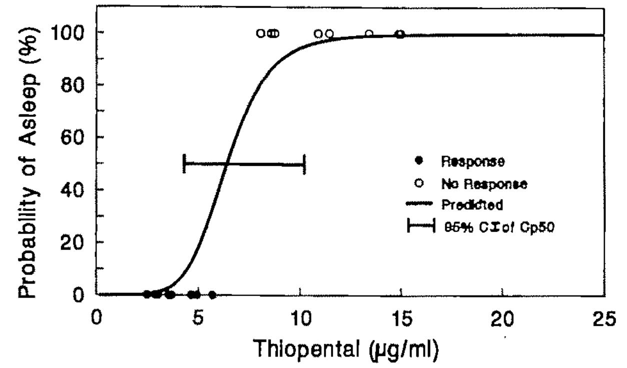

Figure 4. Thiopental plasma concentration at which patients (*n* = 18) were either awake or asleep (lack of response to open eyes to a verbal command) after a 10-min infusion of thiopental and fentanyl maintained at a constant concentration. The fentanyl concentration was maintained at 1.27 ng/mL (SD ±0.5). In the presence of this concentration of fentanyl, the thiopental plasma concentration at which there is a 50% probability of a patient not responding to a verbal command (Cp50) is 7.2 µg/mL (95% confidence interval, 4.8–10.2).

thetics, MAC (minimum alveolar concentration necessary to prevent a somatic response to skin incision in 50% of patients) has provided a measure of potency and has thus allowed the drug interaction of these anesthetics to be clearly defined (14). For intravenous anesthetics, potency is generally defined by the dose-response relationship. The relationship between dose and response can be misleading owing to the complex and time-varying influence of pharmacokinetics and pharmacodynamics (6).

Most previously published work with thiopental has used conventional dosing methodology (1–5,15,16) rather than drug concentration to study drug effect and drug interaction. There may be differences in pharmacokinetics of thiopental (especially related to age) so that the same dose of thiopental may result in markedly different plasma concentrations in different patients (17). Second, variables such as hysteresis affect the relationship between measured drug concentration and concentration at the effect site, therefore altering the relationship between drug concentration measured in plasma and the intensity of the effect produced (6,18). Ideally, the concentration at the effect site is needed to characterize the concentration-response relationship. It is usually not possible to measure the concentration of a drug at the site of action. Both thiopental (6) and fentanyl (18) result in hysteresis of their concentration-effect relationship. Thus, any study in which the plasma concentration is constantly varying (e.g., bolus dose or rapid infusions) will result in a false interpretation of the plasma concentration-effect relationship, unless hysteresis is accounted for by complex mathematical modeling.

Recently, the IC_{50} (concentration required to produce one-half of the maximal EEG, which is derived from an inhibitory Emax model relating the spectral edge of the EEG to the measured arterial concentration of thiopental) has been proposed as a measure of potency for thiopental (6,17,18). The IC_{50}, because it accounts for both pharmacokinetic and pharmacodynamic effects, is an appropriate measure of potency. Different drugs produce different effects on the EEG, and therefore the IC_{50} may not be the ideal measure of potency when trying to establish the interaction between two different drugs. Hypnosis is a common and easily definable clinical end point. It therefore is a convenient measure of effect.

When using a single measure of effect to define the concentration-response relationship, it is still necessary to account for pharmacokinetic and pharmacodynamic influences. This can be done by maintaining the concentration constant for a sufficient period to provide equilibration of drug plasma concentration and effect site concentration. Under steady concentration conditions, the drug concentration at the site of action will, after a set delay (as determined by the drug's keo, where $t_{1/2}$ keo is the half-life for equilibration between plasma concentration and drug effect), be proportional to the plasma concentration and thus allow the determination of a true concentration-effect relationship. To ensure adequate equilibration between plasma concentration and the effect site, the desired plasma concentration was maintained for 10 min. With the keo values determined for thiopental (6) and fentanyl (18), at 10 min the equilibration between plasma and brain concentration would be predicted to be 100% for thiopental and 75% complete for fentanyl. Under these conditions, we determined that the plasma concentration of thiopental necessary to provide a loss of response to a verbal command (i.e., hypnosis) in 50% of our patients was 7.3 µg/mL in the absence or presence of fentanyl (0–2.1 ng/mL). The Cp_{90}(asleep) of thiopental was 9.8 µg/mL. With the development of commercially available CACI devices, the Cp_{90}(asleep) may become a clinically useful value, because it represents the thiopental concentration required to provide loss of consciousness in 90% of patients.

To provide a steady plasma concentration, we used a pharmacokinetic model-driven infusion device that permits drugs to be infused to a desired plasma concentration. Pharmacokinetics vary from patient to patient, and thus any infusion scheme cannot precisely obtain and maintain a desired concentration. From our previous work with CACI, we have found that when using a pharmacokinetic set that tends to neither over nor underpredict the desired concentration, the variation of the predicted to measured concentration in most patients is ±30%. Ideally, the desired concentration should be maintained exactly, but with present technology this is impossible. We therefore had to choose a degree of variability that was both obtainable yet was unlikely to alter the accuracy of calculating the Cp_{50}(asleep). We knew that we could achieve a steady concentration within ±30% in the majority of our patients, and thus we accepted this degree of variability for calculation of the Cp_{50}(asleep) and Cp_{90}(asleep). From our results it would appear that this degree of variability in concentration over the 10-min infusion was adequate to describe the pharmacokinetic dynamic relationship with thiopental. This is confirmed by the one patient who was asleep at 5 min with a thiopental plasma concentration of 7.5 μg/mL and was awake (as would be predicted by the model) at a concentration of 5.6 μg/mL at 10 min.

There are several studies that have investigated either the hypnotic concentration of thiopental or the interaction of thiopental and fentanyl in providing hypnosis. Becker (3) administered a bolus dose of 1.5 mg/kg, followed by a rapid infusion of 1.5 $mg \cdot kg^{-1} \cdot h^{-1}$ of thiopental, and determined the concentration of thiopental to prevent a response to a painful stimulus as 42.2 ± 2.8 μg/mL. The thiopental Cp_{50}(asleep) defined in our study is much lower than that obtained by Becker both because his endpoint was different (loss of response to a painful stimulus), and he did not account for hysteresis. There are several studies that, although not defining the Cp_{50}(asleep), do support the value that we obtained. The plasma concentration of thiopental on awakening after a thiopental infusion was previously reported as 5.9 ± 1.1 μg/mL (19) and 8 μg/mL (20). Both values are very similar to the concentration that we determined to just produce hypnosis in 50% of patients. When a thiopental infusion was used to provide sedation/sleep in patients in an intensive care unit, the measured thiopental plasma concentration at 24–36 h after initiating the infusion was 8.78 μg/mL (21). There have also been several studies in which the EEG and thiopental concentrations have been measured (6,16,22,23). Thiopental produces a biphasic effect on the EEG amplitude, with an initial increase followed by a decrease in amplitude. Early stage 2 of the EEG after thiopental administration is associated with loss of consciousness (6,23). Buhrer et al. (23) found that stage 2 was obtained with a thiopental concentration of 10 μg/mL. Hudson et al. (6) defined the IC_{50} of thiopental as 16 μg/mL. Although this value is higher than the concentration that we determined to provide hypnosis, the EEG endpoint used to define this concentration is greater than that expected to just provide loss of consciousness. Thus, in studies in which a steady concentration was maintained and hysteresis was accounted for, the plasma concentration of thiopental required to provide hypnosis is in general agreement with the value that we have defined as the thiopental Cp_{50}(asleep).

We used venous blood samples for our assessment of the Cp_{50}(asleep). Venous blood concentrations may vary according to the sampling site, and hysteresis with thiopental venous concentrations may be less than that with arterial concentrations (6). Although for both thiopental (22) and fentanyl (7) after a 10-min infusion, venous samples obtained from the arm closely approximate arterial concentrations, it may be preferable to use arterial rather than venous blood samples to relate measured drug concentration to effect.

The second portion of our study investigated the drug interaction of an analgesic concentration of fentanyl on the thiopental Cp_{50}(asleep). The interaction of thiopental and fentanyl has previously been studied (4,5,15,16); however, these studies have investigated this interaction with combinations of bolus doses. We chose to infuse fentanyl to a predicted plasma concentration of 1 ng/mL, because previous studies have suggested that plasma levels of this magnitude are sufficient to provide satisfactory postoperative analgesia (24). Also, in studies determining the MAC reduction of either isoflurane (25) or desflurane (13) by fentanyl, reduction in MAC was very steep between a fentanyl concentration of 0 and 1 ng/mL. We were unable to demonstrate any significant change in the Cp_{50}(asleep) for thiopental in the presence of an analgesic concentration of fentanyl. This is in contrast to several other studies in which bolus doses of fentanyl decreased the induction dose of thiopental (4,5,15,16). The differences between our results and these studies may be due to differences in methodology. In addition, low doses of fentanyl (1.5 μg/kg) resulted in only a small decrease in the thiopental dose (13%) (5), whereas larger fentanyl doses (4 μg/kg) resulted in more pronounced decreases in thiopental requirements for the induction of anesthesia (15,16). Even a dose of 1.5 μg/kg will result in a peak plasma and effect compartment concentration that exceeds 2.0 ng/mL. Thus, a possible explanation for the differences in our findings compared with those of others is that the effects of fentanyl on reducing thiopental requirements to produce sleep are only evident at higher fentanyl concentrations. Certainly, the pharmacodynamic effects of fentanyl (e.g., respiratory depression and analgesia) occur over slightly different plasma concentration ranges, and the dose of fentanyl required to induce loss of consciousness is much higher than that required to produce analgesia. Becker (3), as in our study, found that a small but analgesic dose of meperidine (1.2 mg/kg) did not alter the concentration of thiopental to prevent a response to a painful stimulus. Thus, any interaction of fentanyl and thiopental appears to be minimal at low (analgesic) concentrations but may be additive or synergystic at higher concentrations of fentanyl.

The MAC (awake), the concentration at which 50% of patients respond to command, is not altered by opiates (26,27). This is in contrast to the decrease in MAC (concentration at which 50% of patients do not respond with purposeful movement to skin incision) produced by fentanyl concentrations between 0 and 2 ng/mL (13,25). Thus, although our study has shown a minimal interaction between low fentanyl concentrations and thiopental on hypnosis, this interaction may be markedly different if the endpoint measured is response to skin incision (cf. MAC).

Age has an important influence on the effect of drugs in producing anesthesia (14,17). The MAC of the potent inhaled anesthetics is clearly altered by age (14). Several studies have also demonstrated that the induction dose of thiopental is decreased with increasing age (1,17). This altered sensitivity to thiopental may be due to changes in either pharmacokinetics or pharmacodynamics that occur with increasing age. It was recently shown that the decrease in dose of thiopental is due to changes in the rapid intercompartmental clearance with increasing age rather than an alteration in brain sensitivity (17,28). Our study covered an age range of 18–71 yr, and we also found that age did not affect the determination of the Cp$_{50}$(asleep), thus confirming that the sensitivity of the brain to thiopental is unaltered by increasing age.

Utilization of a pharmacokinetic model-driven infusion system (e.g., CACI), programmed with average pharmocokinetic variables, enables a stable plasma concentration to be obtained. By knowing that hysteresis occurs and using the keo for the drug(s) under study, a constant relationship between plasma concentration and biophase concentration can be established, and the patient's response to a stimulus can be quantified. Thus, the potency of various intravenous anesthetics need no longer be compared in terms of dose; rather, they can be compared in terms of the plasma concentration required to produce or prevent an effect/response in 50% of the patients tested. It is customary to compare the potency of the various inhaled anesthetics in terms of their MAC values. This has greatly improved comparisons made among these anesthetics. The MAC has also enabled drug interactions to be clearly defined with regard to the potent inhaled anesthetics. The methodology used in this study is analogous to that used when determining the MAC for an inhaled anesthetic. The drug is infused over a given time period until a constant plasma and biophase (effect) level is obtained and the response to a given stimulus is measured. The determination of the Cp$_{50}$(asleep) will similarly enable accurate comparisons among the various intravenous anesthetics (and among the opiates) and will allow their interactions to be clearly defined.

Further studies using this methodology are required, first to elucidate the plasma concentration of thiopental at which there is no response to a surgical stimulus (Cp$_{50}$[surgical stimulus]) and second to examine the effects of higher plasma levels of fentanyl both on the Cp$_{50}$(asleep) and the Cp$_{50}$(surgical stimulus) for thiopental. There are also other intravenous drugs used to provide anesthesia, many of which have been reported to have a synergistic interaction when evaluated by their dose-response effects. Our results suggest that further work is required, using methodology similar to ours, to clearly characterize the interaction of the intravenous anesthetics.

In summary, we have used a computer-controlled continuous infusion device to define the Cp$_{50}$(asleep) for thiopental in unpremedicated subjects and demonstrated that fentanyl infused to an analgesic concentration has no effect on the hypnotic concentration of thiopental. This methodology may be extrapolated to elucidate the Cp$_{50}$(asleep) for all of the currently available intravenously administered drugs used to induce anesthesia and thus allow their potencies to be compared in the same way that MAC compares the potencies of the various inhaled anesthetics.

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Effect of Intravenous Clonidine on the Dose of Thiopental Required to Induce Anesthesia

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A randomized, double-blind, controlled trial was conducted to investigate the influence of intravenous clonidine on thiopental dose requirements when used for induction of anesthesia and associated hemodynamic effects. Sixty ASA physical status I or II patients were randomly allocated to one of three treatment groups: normal saline solution (control, $n = 20$); clonidine (2.5 μg/kg, $n = 20$); or clonidine (5 μg/kg, $n = 20$). The test drug was administered 15 min before induction of anesthesia with intravenous thiopental. The dose of thiopental to produce loss of lash reflex was recorded as well as mean arterial blood pressure and heart rate at 3-min intervals up to induction of anesthesia and then at 1-min intervals for 5 min. Significant decreases in thiopental dose were observed in both groups receiving clonidine compared with the control group, but there was no significant difference between clonidine groups. With dosage calculated according to total body mass, the control group required 5.50 ± 1.15 mg/kg (mean ± SD) of thiopental, whereas those who received 2.5 μg/kg of clonidine required 4.15 ± 1.46 mg/kg of thiopental (a reduction of 25%), and those who received 5.0 μg/kg of clonidine required 3.48 ± 1.06 mg/kg of thiopental (a reduction of 37%). When thiopental dose was adjusted for lean body mass, similar reductions were obtained. Clonidine, in both doses, produced more sedation than control, and the 2.5-mg/kg dose produced less sedation than the larger dose. Mean arterial blood pressure was lower in the groups receiving clonidine. There were no significant differences in heart rate among the three groups. If intravenous clonidine is to be used as an adjunct to general anesthesia, appropriate adjustments to the dosage of intravenous thiopental will be required.

(Anesth Analg 1992;75:530–5)

Clonidine is an α_2-adrenergic receptor agonist that acts centrally to decrease sympathetic outflow. The use of clonidine as an antihypertensive is associated with sedation in the acute clinical situation, and because similar drugs are used as anesthetics in veterinary practice (1), much interest has focused on the potential anesthetic properties of this drug in humans. Orally administered clonidine decreases anesthetic requirements for fentanyl (2), droperidol (3), and isoflurane (4), but there is limited information on its effects when given by the more rapid and reliable intravenous route.

Several drugs, such as fentanyl (5) or midazolam (6,7), are often administered intravenously in conjunction with thiopental to decrease thiopental dosage requirements, although data on hemodynamic stability are limited. The pharmacodynamic profile of clonidine suggests that it may also be suitable for this purpose, especially because it produces minimal respiratory depression (8) and possesses analgesic properties (9,10). There are many other potentially useful effects of clonidine during anesthesia, including sympatholysis, as evidenced by attenuation of the pressor response to intubation (11), amelioration of postoperative hypertension and tachycardia (12), and decreased circulating levels of norepinephrine (3) and β-endorphin (13). In addition, intraoperative hemodynamic stability in patients undergoing coronary bypass surgery has been reported (14).

To examine (a) whether intravenous clonidine could be safely administered before induction of anesthesia and (b) the effect on thiopental requirements, we conducted a randomized, double-blind, controlled trial comparing two doses of clonidine (2.5 and 5 μg/kg) administered intravenously 15 min before induction of anesthesia. We also documented the effects of clonidine and the combination of clonidine and thiopental on mean arterial blood pressure (MABP) and heart rate (HR).

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Methods

Sixty patients aged 18–50 yr of ASA physical status I or II who presented for elective surgery were accepted for this study. Patients receiving sedatives, opiates, or medication affecting the cardiovascular system were excluded, as were those with untreated hypertension (systolic blood pressure >180 mm Hg) and obesity (>50% fat) likely to cause difficulty with mask ventilation. The study was approved by the Hospital Ethics Committee, and all patients gave informed consent.

The total body mass (TBM) of each patient was measured preoperatively. Lean body mass (LBM) was then determined using TBM (kg), height (cm), and girth at the umbilicus (cm), as described previously by Wolfsohn and Joshi (15):

$$\% \text{ Fat} = 90 - (\text{Height} - \text{Girth})/0.79;$$

$$\text{LBM} = [(100 - \% \text{ Fat})/100] \times \text{TBM}.$$

No premedication was administered. On arrival in the operating suite, an intravenous infusion of lactated Ringer's solution was begun. Routine monitoring, including a Dinamap (Critikon) for noninvasive measurement of blood pressure, was used. Random-number tables were used to allocate the 60 patients to three groups of equal size. The control group received normal saline solution (10 mL); the two study groups received clonidine (Catapress, Boehringer) (2.5 or 5.0 μg/kg) diluted in 10 mL of normal saline solution. Drugs were prepared independently in a 10-mL syringe marked "study drug," and the administering anesthesiologist remained unaware of the identity of the drug.

Baseline arterial blood pressure, HR, and oxygen saturation were recorded. The "study drug" was then administered intravenously over 60 s. The electrocardiograph was continuously observed, and oxygen saturation, MABP, and HR were monitored and recorded every 3 min for 15 min. At 15 min, just before administration of thiopental, sedation was graded 0–5 (0 = awake, anxious; 1 = awake, calm; 2 = drowsy, eyes open; 3 = mild sedation, eyes closed, responds to verbal command; 4 = moderate sedation, unresponsive to verbal command, responds to light touch; 5 = profound sedation, unresponsive) (16).

After 15 min, 2.5% thiopental was injected at a rate of 50 mg every 15 s until loss of the eyelash reflex occurred. The patient was then allowed to breathe 100% oxygen spontaneously for 5 min while the MABP, HR, and oxygen saturation were measured every minute. Thereafter, the anesthetic was conducted as indicated for the surgery. At the end of each case, the anesthetic records were reviewed, and any untoward effects were noted.

Table 1. Demographic Data of 60 Patients Undergoing Elective Surgery

	Control group (n = 20)	Clonidine group (2.5 μg/kg) (n = 20)	Clonidine group (5.0 μg/kg) (n = 20)
M/F	11/9	10/10	9/11
Age (yr)	27.1 ± 7.7	28.4 ± 6.4	31.0 ± 8.5
TBM (kg)	70.6 ± 11.3	68.9 ± 10.0	71.8 ± 15.0
LBM (kg)	55.5 ± 9.2	55.2 ± 9.1	55.3 ± 13.4
% Fat	19.3 ± 10.5	19.7 ± 5.6	22.6 ± 11.4

M/F, male/female; TBM, total body mass; LBM, lean body mass.
Values are mean ± SD.

SuperANOVA (Abacus Concepts, Berkley, Calif.) and BMDP (Statistical Software, Berkley, Calif.) were used for statistical analyses. The level of significance was set at $P < 0.05$. All data are expressed as mean ± SEM, except dosage of thiopental, which is expressed as mean ± SD. Demographic data were analyzed with analysis of variance. Because of the sequential nature of the observations, hemodynamic data were analyzed with a repeated measures analysis of variance (17). Data obtained in the 15 min after clonidine administration were analyzed separately from data obtained after induction of anesthesia. Sedation scores were compared with the Mann-Whitney U-test.

Results

There were no significant differences among the three treatment groups with regard to mean age, gender, TBM, LBM, and percent body fat (Table 1).

Intravenous clonidine significantly decreased the dose of thiopental required to produce loss of eyelash reflex compared with control, whether dosage was calculated according to TBM or LBM (Figure 1). Control patients required 5.50 ± 1.15 mg/kg TBM (mean ± SD) or 7.06 ± 1.72 mg/kg LBM. A clonidine dose of 2.5 mg/kg reduced the thiopental requirement by 25% (4.15 ± 1.46 mg/kg TBM and 5.21 ± 1.51 mg/kg LBM). A clonidine dose of 5.0 mg/kg reduced the thiopental requirement by 37% (3.48 ± 1.06 mg/kg TBM) and 36% (4.55 ± 1.31 mg/kg LBM). There was no significant difference between the two clonidine groups in terms of thiopental dose. With 40 subjects, 80% power ($\beta = 0.20$) would detect a change >0.8 mg/kg. Because we believe that clinically significant changes are greater than this, the power was more than adequate for this analysis.

Mean sedation scores at 15 min, just before thiopental administration, were 0.85 ± 0.15 for the control group, 2.0 ± 0.20 for the 2.5-mg/kg group, and 2.55 ± 0.17 for the 5.0-mg/kg group. There was a highly significant difference between the control

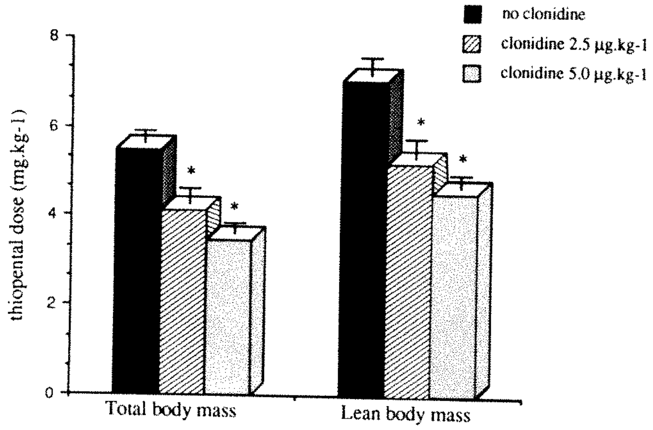

Figure 1. The effect of intravenous clonidine on the induction dose requirement of thiopental with thiopental dosage based on total body mass and lean body mass (mean ± SEM). $^*P < 0.05$ compared with no-clonidine group.

group and each of the clonidine groups ($P = 0.0001$ for both comparisons); however, the difference between the two clonidine groups only just reached statistical significance ($P = 0.0478$).

There was no significant difference among the three groups in baseline MABP or HR. The relationship between MABP and time for the three groups is shown in Figure 2. The MABP decreased significantly with time in all three groups until induction with thiopental. After induction of anesthesia, MABP continued to decrease in each group, but this was not significant in any group. Patients receiving clonidine had significantly lower MABP than control patients at 3, 6, 9, 12, and 15 min after administration. After induction, no statistically significant differences were found among the three groups. No difference was demonstrated between the two doses of clonidine at any time either before or after induction.

Figure 3 shows the relationship between HR and time for the three groups. The interaction between HR and time was statistically significant; HR decreased in all groups until just before induction. The administration of 2.5 or 5.0 µg/kg of clonidine did not have a significant effect on HR at any time.

Discussion

Intravenous clonidine administered before induction of anesthesia effectively decreased thiopental requirements and provided sedation. No patient complained of an unpleasant experience, and there were no adverse side effects. Our results confirm other work demonstrating the anesthetic-sparing effect of clonidine (2–4). Although this effect may be due solely to a decrease in central noradrenergic transmission, evidence is now accumulating to the effect that the α_2-receptor itself may mediate an anesthetic response (18). In animals, an intravenous dose of 5.0 mg/kg reduced the minimal anesthetic concentration (MAC) of halothane in the dog by 42% (19) and, in the rat, a dose of 10 mg/kg reduced MAC by 32% (20).

There are limited data on the use of the intravenous preparation as an anesthetic supplement in humans. It has been shown recently by Carabine et al. (11) that 0.625 and 1.25 µg/kg of clonidine attenuates the response to endotracheal intubation and decreases thiopental requirements (15% and 28%, respectively) while producing no significant changes in MABP or HR in the 15 min after its administration. Although we used larger doses of clonidine, we observed a smaller decrease in thiopental dose requirement for the 2.5-µg/kg group (25%) than the 1.25-mg/kg group (28%) of the Carabine et al. (11) study. This was probably due to the temazepam premedication used in the latter study.

Previous studies have shown that the administration of thiopental on the basis of LBM results in much less variation in response than when TBM is used to calculate dosage (15). In this study, the reduction in thiopental requirement was similar whether TBM or LBM was used. This may have resulted from the patients having relatively low body fat with little variation within each group.

The decreased MABP in the clonidine groups raises the possibility that this may have unblinded the study and introduced observer bias. However, because the changes in hemodynamic variables in all groups were minimal in the time leading up to thiopental administration, and because of the manner in which the study was conducted, we remain confident that no such bias was introduced.

It appears that increasing doses of clonidine produce a progressive reduction in thiopental requirements. This is most certainly a pharmacodynamic interaction, because we are unaware that clonidine has any effect on thiopental redistribution. Whether clonidine has the capacity to further reduce anesthetic requirements in humans when given in doses >5 mg/kg remains to be discovered. It has been shown that sedation and plasma concentration of clonidine are positively correlated up to 1.5–2.0 ng/mL, but that above this, the maximal level of sedation persists unchanged (21). It may be that the dose-response curve of clonidine reaches a plateau at high doses.

Investigating the optimal dose of clonidine must be done with caution because clonidine has significant hypotensive properties. Fortunately, the hypotensive effect of clonidine in normotensive patients appears to be less than in patients with hypertension (21). The normotensive patients studied here demonstrated significant but clinically tolerable decreases in

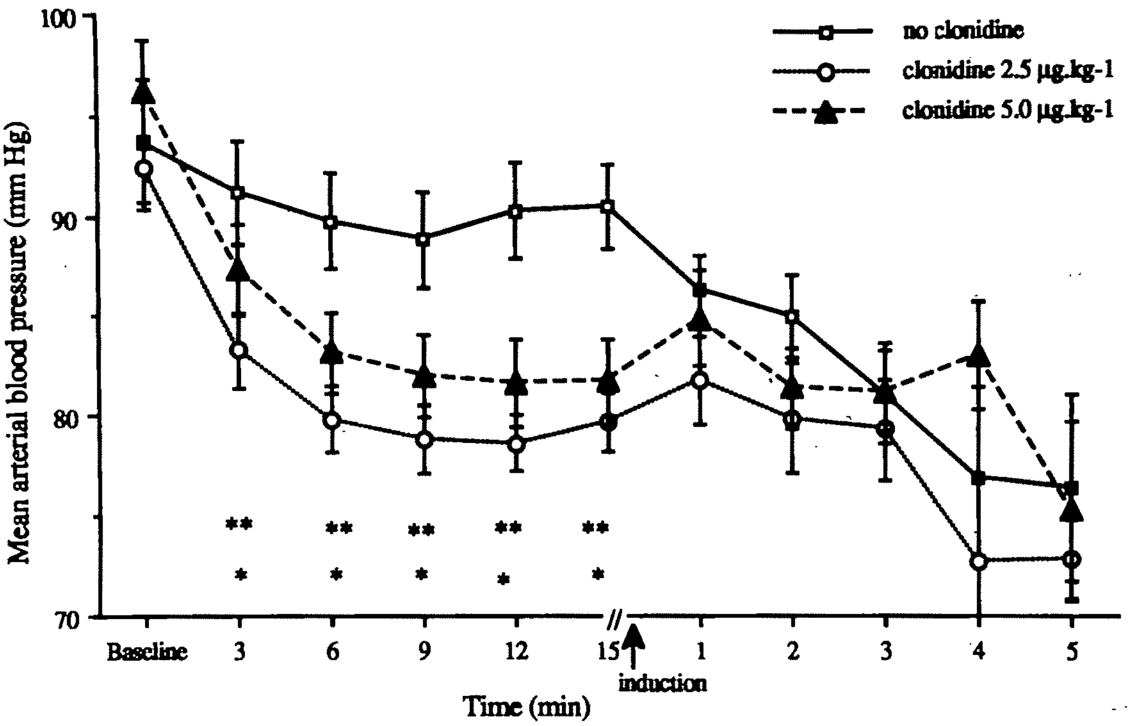

Figure 2. Relationship between mean arterial blood pressure and time. *$P < 0.05$ when 2.5 μg/kg clonidine group was compared with no-clonidine group. **$P < 0.05$ when 5.0 mg/kg clonidine group was compared with no-clonidine group.

MABP, and there was no difference among the three groups in the hemodynamic response to thiopental administration. Of importance, there was no pronounced decrease in MABP caused by the combination of the two drugs, although the hypotensive effects of clonidine may well outlast those of thiopental.

The two doses of clonidine used in this study did not differ significantly in their hypotensive effects. This may be explained by the fact that at higher blood levels of clonidine, peripheral α-receptor stimulation is more prominent than at lower levels and causes an increase in arterial blood pressure owing to a rise in systemic vascular resistance (1). This may be due to partial agonist activity at postsynaptic peripheral α_1- or α_2-receptors. The central α_2-receptor effect, which is responsible for the long-term antihypertensive effects of clonidine, occurs at lower blood levels. We demonstrated no significant effect of clonidine on HR in our healthy subjects. A relative bradycardia has been demonstrated by other workers, but the magnitude of this is usually small (22).

Although it would have been desirable to study hemodynamic variables throughout the intraoperative period, the surgery for which our patient population presented was too diverse to allow a standard anesthetic regime and thus continue the study intraoperatively. Review of the anesthetic records did, however, reveal the occurrence of hypotension and bradycardia. In the control group, there were 7 of 20 patients in whom the systolic blood pressure decreased below 100 mm Hg; in 5 of 20 patients, the HR was recorded as <60 beats/min. None of these patients received treatment. In contrast, 13 of 20 patients in the 2.5-μg/kg clonidine group and 15 of 20 patients in the 5.0-μg/kg clonidine group recorded systolic blood pressure <100 mm Hg during the intraoperative period, and 7 of 20 and 11 of 20, respectively, recorded HR as <60 beats/min. Four patients in the low-dose group and three patients in the larger dose group received treatment for either hypotension or bradycardia. In no case was any adverse outcome recorded.

Many factors may lead to circulatory instability in the intraoperative period. The addition of nitrous oxide, volatile anesthetics, and opiates, movement of the patient from the anesthetic to the operating room, and the effects of surgery may all have contributed. It may be necessary to alter the management of anesthesia after the use of clonidine in light of the intrinsic anesthetic properties of this drug. Alternatively, clonidine may have been the cause of hypotension on its own, because the maximal hypotensive effect may not occur until approximately 90 min after injection (22). The design of this study did not allow an evaluation of the timing of the maximal point of cardiovascular effects of intravenous clonidine.

Clonidine (2.5 mg/kg) proved to be an effective

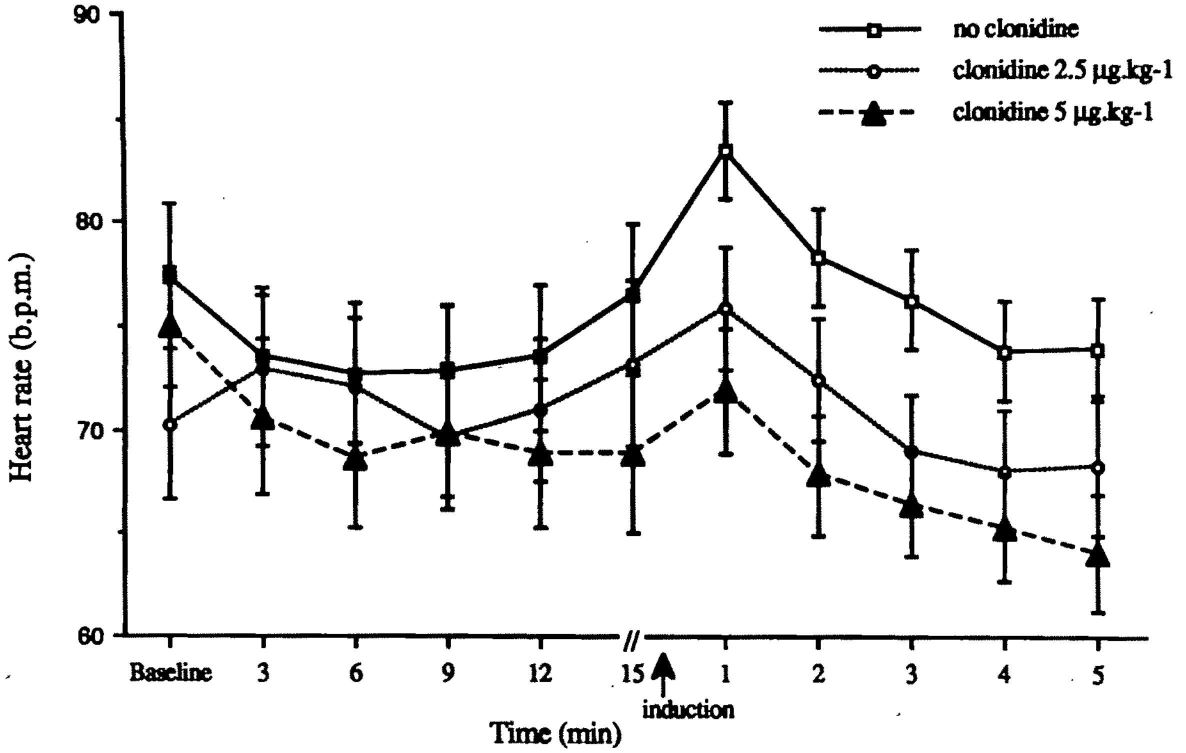

Figure 3. Relationship between heart rate and time. No significant differences between groups. b.p.m., beats/min.

sedative, and only a small incremental effect was gained by increasing the dose. This result is consistent with the thiopental requirements and hemodynamic effects, which also displayed modest changes at the larger dose.

In conclusion, intravenous clonidine administered before administration of thiopental diminishes anesthetic requirements and provides sedation. Significant decreases in MABP may occur with little change in HR. Although there is no major early hemodynamic instability, hypotension and bradycardia may occur later during the intraoperative course. Our results suggest that limited advantage may be gained by increasing the dose of clonidine to 5.0 mg/kg. Intravenous clonidine may be safely administered before induction of anesthesia, allowing further evaluation of the many useful effects during general anesthesia.

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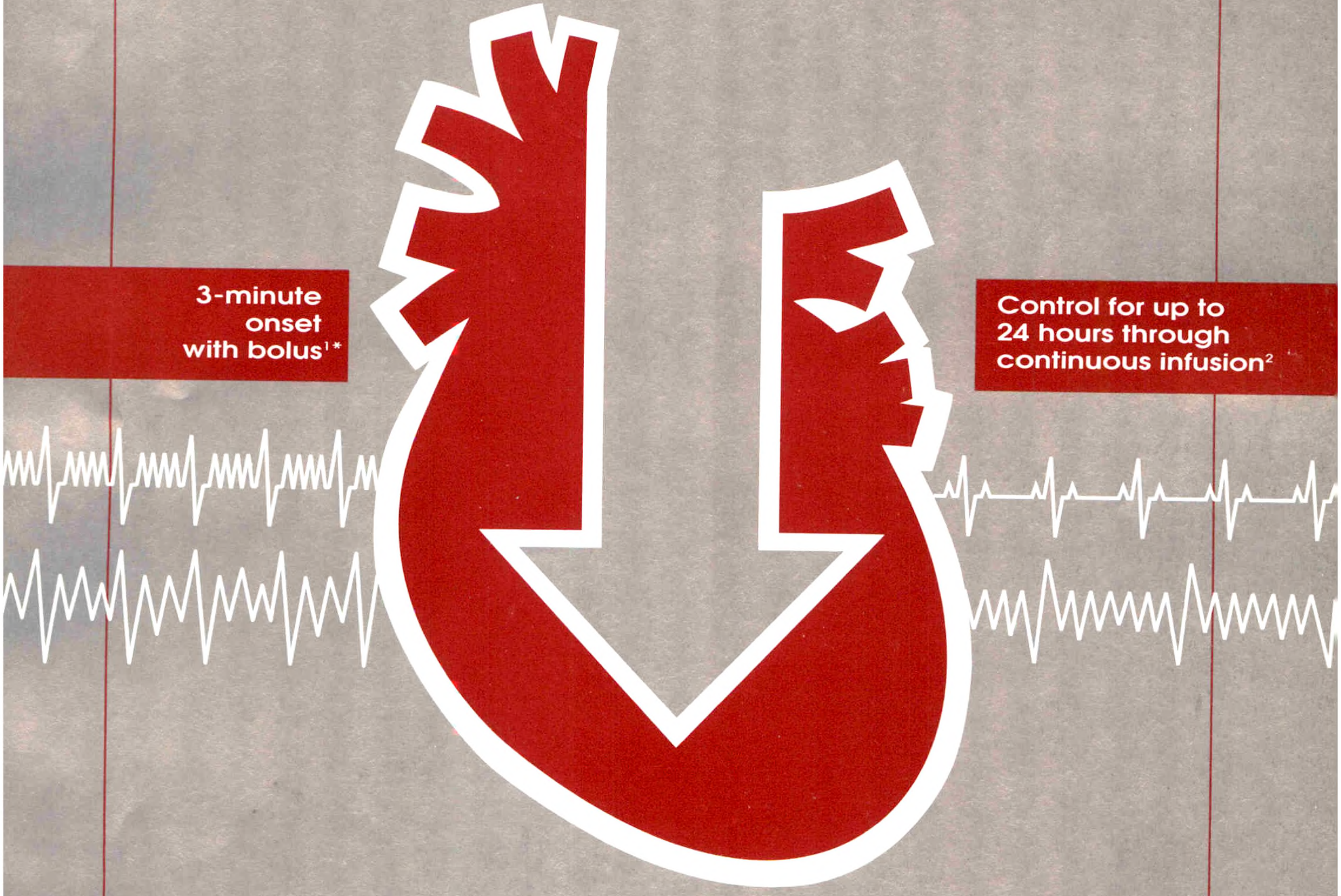
Now for heart rate control during atrial fibrillation and flutter

CARDIZEM® Injectable
(diltiazem hydrochloride)
BOLUS INFUSION
5 mg/mL



3-minute onset with bolus[1]*

Control for up to 24 hours through continuous infusion[2]

Heart rate control that is

FAST, SAFE, AND CONTINUOUS[1,2†]

Cardizem Injectable is indicated for temporary control of rapid ventricular rate during atrial fibrillation and flutter; rarely converts to normal sinus rhythm; should be used with continuous monitoring of ECG and blood pressure to avoid hypotension or bradycardia. Infusion rate/dose should be regulated accordingly. A defibrillator and emergency equipment should be readily available.

*Symptomatic hypotension (3.2%) or flushing (1.7%) occurs most often during or immediately following bolus injection. †Contraindications: atrial fibrillation and flutter patients with WPW or short PR syndrome; sick sinus syndrome or second- or third-degree AV block, except with a functioning pacemaker; severe hypotension or shock; hypersensitivity; recent IV beta-blockers; ventricular tachycardia.

Please see the brief summary of prescribing information on an adjacent page.

CIVAH497/A8114

6491E2

CARDIZEM® Injectable

(diltiazem hydrochloride)

BOLUS INFUSION

CONVENIENT DOSAGE

1 Beginning treatment as

BOLUS: 0.25 mg/kg actual body weight **over 2 minutes**

20 mg average patient

2 If response is inadequate, wait 15 minutes

BOLUS: 0.35 mg/kg actual body weight **over 2 minutes**

25 mg average patient

3 Treatment as

INFUSION:

10* to 15 mg/hr

*5 mg/hr may be appropriate starting infusion for some patients.

BRIEF SUMMARY

CARDIZEM® Injectable

(diltiazem hydrochloride)

INDICATIONS AND USAGE

CARDIZEM Injectable (diltiazem hydrochloride) is indicated for the following:

1. ***Atrial Fibrillation or Atrial Flutter.*** Temporary control of rapid ventricular rate in atrial fibrillation or atrial flutter. It should not be used in patients with atrial fibrillation or atrial flutter associated with an accessory bypass tract such as in Wolff-Parkinson-White (WPW) syndrome or short PR syndrome.
2. ***Paroxysmal Supraventricular Tachycardia.*** Rapid conversion of paroxysmal supraventricular tachycardias (PSVT) to sinus rhythm. This includes AV nodal reentrant tachycardias and reciprocating tachycardias associated with an extranodal accessory pathway such as the WPW syndrome or short PR syndrome. Unless otherwise contraindicated, appropriate vagal maneuvers should be attempted prior to administration of CARDIZEM Injectable.

The use of CARDIZEM Injectable for control of ventricular response in patients with atrial fibrillation or atrial flutter or conversion to sinus rhythm in patients with PSVT should be undertaken with caution when the patient is compromised hemodynamically or is taking other drugs that decrease any or all of the following: peripheral resistance, myocardial filling, myocardial contractility, or electrical impulse propagation in the myocardium.

For either indication and particularly when employing continuous intravenous infusion, the setting should include continuous monitoring of the ECG and frequent measurement of blood pressure. A defibrillator and emergency equipment should be readily available.

In domestic controlled trials in patients with atrial fibrillation or atrial flutter, bolus administration of CARDIZEM Injectable was effective in reducing heart rate by at least 20% in 95% of patients. CARDIZEM Injectable rarely converts atrial fibrillation or atrial flutter to normal sinus rhythm. Following administration of one or two intravenous bolus doses of CARDIZEM Injectable, response usually occurs within 3 minutes and maximal heart rate reduction generally occurs in 2 to 7 minutes. Heart rate reduction may last from 1 to 3 hours. If hypotension occurs, it is generally short-lived, but may last from 1 to 3 hours.

A 24-hour continuous infusion of CARDIZEM Injectable in the treatment of atrial fibrillation or atrial flutter maintained at least a 20% heart rate reduction during the infusion in 83% of patients. Upon discontinuation of infusion, heart rate reduction may last from 0.5 hours to more than 10 hours (median duration 7 hours). Hypotension, if it occurs, may be similarly persistent.

In the controlled clinical trials, 3.2% of patients required some form of intervention (typically, use of intravenous fluids or the Trendelenburg position) for blood pressure support following CARDIZEM Injectable.

In domestic controlled trials, bolus administration of CARDIZEM Injectable was effective in converting PSVT to normal sinus rhythm in 88% of patients within 3 minutes of the first or second bolus dose.

Symptoms associated with the arrhythmia were improved in conjunction with decreased heart rate or conversion to normal sinus rhythm following administration of CARDIZEM Injectable.

CONTRAINDICATIONS

CARDIZEM Injectable is contraindicated in:

1. Patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker.
2. Patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker.
3. Patients with severe hypotension or cardiogenic shock.
4. Patients who have demonstrated hypersensitivity to the drug.
5. Intravenous diltiazem and intravenous beta-blockers should not be administered together or in close proximity (within a few hours).
6. Patients with atrial fibrillation or atrial flutter associated with an accessory bypass tract such as in WPW syndrome or short PR syndrome.

   As with other agents which slow AV nodal conduction and do not prolong the refractoriness of the accessory pathway (eg, verapamil, digoxin), in rare instances patients in atrial fibrillation or atrial flutter associated with an accessory bypass tract may experience a potentially life-threatening increase in heart rate accompanied by hypotension when treated with CARDIZEM Injectable. As such, the initial use of CARDIZEM Injectable should be, if possible, in a setting where monitoring and resuscitation capabilities, including DC cardioversion/defibrillation, are present (see OVERDOSAGE). Once familiarity of the patient's response is established, use in an office setting may be acceptable.
7. Patients with ventricular tachycardia. Administration of other calcium channel blockers to patients with wide complex tachycardia (QRS ≥ 0.12 seconds) has resulted in hemodynamic deterioration and ventricular fibrillation. It is important that an accurate pretreatment diagnosis distinguish wide complex QRS tachycardia of supraventricular origin from that of ventricular origin prior to administration of CARDIZEM Injectable.

WARNINGS

1. **Cardiac Conduction.** Diltiazem prolongs AV nodal conduction and refractoriness that may rarely result in second- or third-degree AV block in sinus rhythm. Concomitant use of diltiazem with agents known to affect cardiac conduction may result in additive effects (see Drug Interactions). If high-degree AV block occurs in sinus rhythm, intravenous diltiazem should be discontinued and appropriate supportive measures instituted (see OVERDOSAGE).
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function and in patients with a compromised myocardium, such as severe CHF, acute MI, and hypertrophic cardiomyopathy, have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Administration of oral diltiazem in patients with acute myocardial infarction and pulmonary congestion documented by x-ray on admission is contraindicated. Experience with the use of CARDIZEM Injectable in patients with impaired ventricular function is limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM Injectable therapy may occasionally result in symptomatic hypotension (3.2%). The use of intravenous diltiazem for control of ventricular response in patients with supraventricular arrhythmias should be undertaken with caution when the patient is compromised hemodynamically. In addition, caution should be used in patients taking other drugs that decrease peripheral resistance, intravascular volume, myocardial contractility or conduction.
4. **Acute Hepatic Injury.** In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted following oral diltiazem. Therefore, the potential for acute hepatic injury exists following administration of intravenous diltiazem.
5. **Ventricular Premature Beats (VPBs).** VPBs may be present on conversion of PSVT to sinus rhythm with CARDIZEM Injectable. These VPBs are transient, are typically considered to be benign, and appear to have no clinical significance. Similar ventricular complexes have been noted during cardioversion, other pharmacologic therapy, and during spontaneous conversion of PSVT to sinus rhythm.

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. The drug should be used with caution in patients with impaired renal or hepatic function (see WARNINGS). High intravenous dosages (4.5 mg/kg tid) administered to dogs resulted in significant bradycardia and alterations in AV conduction. In subacute and chronic dog and rat studies designed to produce toxicity, high oral doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver, which were reversible when the drug was discontinued. In dogs, oral doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Dermatologic events progressing to erythema multiforme and/or exfoliative dermatitis have been infrequently reported following oral diltiazem. Therefore, the potential for these dermatologic reactions exists following exposure to intravenous diltiazem. Should a dermatologic reaction persist, the drug should be discontinued.

Drug Interactions. Due to potential for additive effects, caution is warranted in patients receiving CARDIZEM Injectable concomitantly with any agent(s) known to affect cardiac contractility and/or SA or AV node conduction (see WARNINGS).

As with all drugs, care should be exercised when treating patients with multiple medications. CARDIZEM undergoes extensive metabolism by the cytochrome P-450 mixed function oxidase system. Although specific pharmacokinetic drug-drug interaction studies have not been conducted with single intravenous injection or constant rate intravenous infusion, coadministration of CARDIZEM Injectable with other agents which primarily undergo the same route of biotransformation may result in competitive inhibition of metabolism.

Digitalis: Intravenous diltiazem has been administered to patients receiving either intravenous or oral digitalis therapy. The combination of the two drugs was well tolerated without serious adverse effects. However, since both drugs affect AV nodal conduction, patients should be monitored for excessive slowing of the heart rate and/or AV block.

Beta-blockers: Intravenous diltiazem has been administered to patients on chronic oral beta-blocker therapy. The combination of the two drugs was generally well tolerated without serious adverse effects. If intravenous diltiazem is administered to patients receiving chronic oral beta-blocker therapy, the possibility for bradycardia, AV block, and/or depression of contractility should be considered (see CONTRAINDICATIONS). ***Oral*** administration of diltiazem with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. In vitro, propranolol appears to be displaced from its binding sites by diltiazem.

Anesthetics: The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium blockers should be titrated carefully.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats at oral dosage levels of up to 100 mg/kg/day, and a 21-month study in mice at oral dosage levels of up to 30 mg/kg/day showed no evidence of carcinogenicity. There was also no mutagenic response in vitro or in vivo in mammalian cell assays or in vitro in bacteria. No evidence of impaired fertility was observed in a study performed in male and female rats at oral dosages of up to 100 mg/kg/day.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of oral doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended oral antianginal therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human oral antianginal dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. Diltiazem is excreted in human milk. One report with oral diltiazem suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

The following adverse reaction rates are based on the use of CARDIZEM Injectable in over 400 domestic clinical trial patients with atrial fibrillation/flutter or PSVT under double-blind or open-label conditions. Worldwide experience in over 1,300 patients was similar.

Adverse events reported in controlled and uncontrolled clinical trials were generally mild and transient. Hypotension was the most commonly reported adverse event during clinical trials. Asymptomatic hypotension occurred in 4.3% of patients. Symptomatic hypotension occurred in 3.2% of patients. When treatment for hypotension was required, it generally consisted of administration of saline or placing the patient in the Trendelenburg position. Other events reported in at least 1% of the diltiazem-treated patients were injection site reactions (eg, itching, burning)—3.9%, vasodilation (flushing)—1.7%, and arrhythmia (junctional rhythm or isorhythmic dissociation)—1.0%.

In addition, the following events were reported infrequently (less than 1%):

Cardiovascular:	Atrial flutter, AV block first degree, AV block second degree, bradycardia, chest pain, congestive heart failure, sinus pause, sinus node dysfunction, syncope, ventricular arrhythmia, ventricular fibrillation, ventricular tachycardia.
Dermatologic:	Pruritus, sweating.
Gastrointestinal:	Constipation, elevated SGOT or alkaline phosphatase, nausea, vomiting.
Nervous System:	Dizziness, paresthesia.
Other:	Amblyopia, asthenia, dry mouth, dyspnea, edema, headache, hyperuricemia.

Although not observed in clinical trials with CARDIZEM Injectable, other reactions associated with oral diltiazem may occur.

Product information as of October 1991

MARION MERRELL DOW INC.
PRESCRIPTION PRODUCTS DIVISION
KANSAS CITY, MO 64114

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CARDIZEM INJECTABLE...HEART RATE CONTROL THAT IS FAST, SAFE, AND CONTINUOUS

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Lack of Interaction Between Propofol and Vecuronium

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We estimated the potency of vecuronium and measured the onset and duration of its action during total intravenous anesthesia with propofol to examine the possibility of any interaction between these two drugs. Propofol infusion was administered according to a three-step dosage scheme, and neuromuscular block was monitored by measuring the force of contraction of the adductor pollicis muscle after single-twitch stimulation of the ulnar nerve at 0.1 Hz. A control group of patients were similarly studied during anesthesia with thiopental, nitrous oxide, oxygen, and fentanyl. The ED_{50} and ED_{95} (dose required to produce a 50% and 95% depression of twitch tension, respectively) of vecuronium in patients given total intravenous anesthesia (n = 24) were 24 (22–27, 95% confidence limits) and 41 (37–48, 95% confidence limits) μg/kg, respectively, and in the control group (n = 24), 20 (17–24) and 39 (34–37) μg/kg, respectively. The onset of action of an 80-μg/kg dose (2 × ED_{95}) of vecuronium was 3.6 ± 1.2 and 4.1 ± 1.7 min (mean ± SD), in the propofol (n = 10) and control (n = 10) groups, respectively. The respective times to recovery of the twitch height to 25% of control and the recovery indices (25%–75% recovery of twitch height) in the propofol versus control groups were 28.3 ± 6.6 and 28.0 ± 1.7 min and 13.3 ± 6.8 and 15.4 ± 11.9 min, respectively. There were no significant differences in any of the measured variables between the propofol and control groups, indicating the lack of any interaction between propofol and vecuronium.

(Anesth Analg 1992;75:536–8)

Propofol was originally formulated in Cremophor but now is formulated as an emulsion in soybean oil and egg phosphatide. The original formulation of propofol in Cremophor may potentiate a vecuronium neuromuscular blockade in both experimental and clinical settings (1,2). Lack of significant interaction has been reported between the emulsion formulation of propofol and vecuronium (3,4). However, a cumulative instead of a single dose-response method for estimating the potency of vecuronium was used in one study (3), whereas only a single induction dose of propofol and a single relatively small dose of vecuronium were used in the other (4). Our study was designed to assess any interaction between the currently used emulsion formulation of propofol and vecuronium in humans by first estimating the potency of vecuronium using a single-dose method and then measuring the onset and duration of its action during total intravenous anesthesia with propofol.

Methods

Sixty-eight adult patients, aged 18–65 yr, undergoing body surface operations were included in the study after they gave their informed consent and after the approval of the Research Ethical Committee. All patients conformed to ASA physical status class I or II, and those with a weight >120% of ideal or on medication known to interact with neuromuscular blocking agents were excluded. Premedication consisted of oral diazepam (10 mg) administered 90 min preoperatively. All patients were monitored in the usual manner. Ventilation was adjusted to end-tidal carbon dioxide concentration of 4.5%–5.5%.

Patients were randomly allocated to be anesthetized with either a continuous propofol infusion (propofol group) and ventilation with air and oxygen or thiopental with nitrous oxide and oxygen (control group). Both groups received fentanyl (2–3 μg/kg) at induction, followed by further increments if required. In the propofol group, anesthesia was induced with a dose of 2.5 mg/kg and maintained with an infusion of propofol at a starting rate of

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The results of this study were presented at the Annual Meeting of the American Society of Anesthesiologists, October 1990, Las Vegas, Nevada, and an abstract was published in Anesthesiology 1990;73:A899.

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10 mg·kg^{-1}·h^{-1}, which was reduced at intervals of 10 min each to 8 and 6 mg·kg^{-1}·h^{-1} and then maintained at that rate, as previously reported by Roberts et al. (5). In the control group, anesthesia was induced with thiopental (4–5 mg/kg) and maintained with 70% nitrous oxide in oxygen and fentanyl as required.

The study was conducted in two phases. In phase I, 48 patients, in two groups of 24 each, were studied for estimation of potency of vecuronium during the two anesthetic techniques by constructing dose-response curves. After induction of anesthesia, the ulnar nerve was stimulated at the wrist with supramaximal stimuli at a frequency of 0.1 Hz and the resultant force of contraction of the adductor pollicis muscle was recorded with a force transducer and a neuromuscular function analyzer (Myograph 2000, Biometer Ltd.). After a 10-min stabilization period, eight patients within each anesthetic technique were randomly allocated to receive a bolus dose of 20, 30, or 40 μg/kg of vecuronium, and maximal block was allowed to supervene, regardless of the time taken to achieve it. An arc-sine transformation of the data relating to twitch height was carried out, as used previously to allow analysis of the response between 0% and 100% block (6). Dose-response curves were constructed to allow linear regression analysis to be performed and ED_{50} and ED_{95} (dose required to produce a 50% and 95% depression of twitch tension, respectively) determined.

In the second phase of the study, 80 μg/kg of vecuronium was administered as a single bolus dose to 10 patients, each anesthetized with the two techniques after baseline neuromuscular monitoring was established along the same lines as in phase I. The times to onset of maximal block and to recovery of the twitch height to 25% and 75% of control (for estimating the recovery index) were determined. Analysis of variance, analysis of covariance, and *t*-tests were used to assess the statistical significance of the results, which was accepted at the 5% level.

Results

The groups were comparable as to age and weight in both phases of the study. The dose-response curves as shown in Figure 1 are close to each other. The lines did not differ significantly in their slopes. The derived values of ED_{50} and ED_{95} are given in Table 1. The ED_{50} values of 24 and 20 μg/kg and the ED_{95} values of 41 and 39 μg/kg, in the propofol and control groups respectively were not significantly different.

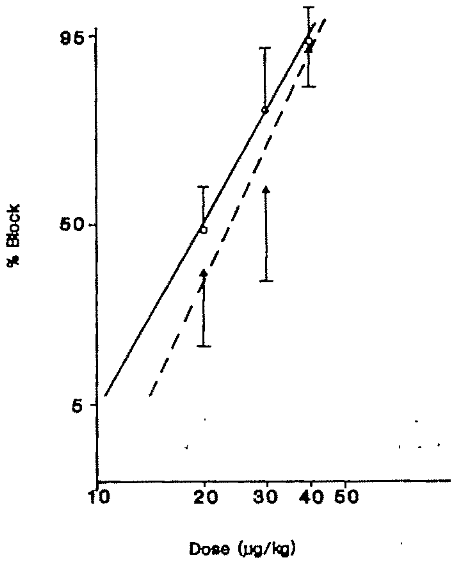

Figure 1. Dose-response curves for vecuronium during anesthesia with propofol (▲—▲) and with thiopental-nitrous oxide-oxygen-fentanyl (○—○). The *points* are the average degree of block obtained with each dose and the *bars* represent standard deviation.

Table 1. Patient Characteristics and Estimated ED_{50} and ED_{95} (95% confidence limits) in the Propofol and Control Groups

	Propofol group (n = 24)	Control group (n = 24)
Age (yr)	49 (15.9)	42 (14.3)
Weight (kg)	69 (13.9)	74 (8.4)
ED_{50} (μg/kg)	24 (22–27)	20 (17–24)
ED_{95} (μg/kg)	41 (37–48)	39 (34–37)

ED_{50}, ED_{95}, dose required to produce a 50% and 95% depression of twitch tension, respectively.
Mean (±SD).

Table 2. Patient Characteristics and Results From the Onset and Duration Phase of the Study

	Propofol group (n = 10)	Control group (n = 10)
Age (yr)	46 (15.2)	46 (15.9)
Weight (kg)	71 (10.5)	67 (11.1)
Time to maximal block (min)	3.6 (1.2)	4.1 (1.7)
Time to return of T-1 to 25% (min)	28.3 (6.6)	28 (1.7)
Recovery index (min)	13.3 (6.8)[a]	15.4 (11.9)[b]

Mean (±SD).
[a] Nine patients.
[b] Seven patients.

The time to maximal block (100% in all cases) was similar between the groups (3.6 and 4.1 min in the propofol and control groups, respectively) without any significant difference. The time to 25% recovery of twitch height (≈28 min) and the recovery indices (13–15 min) also showed no significant difference between the groups (Table 2).

Discussion

Our results showed no differences in the estimates of potency or the onset and duration of action of vecuronium when used in single doses during propofol-fentanyl anesthesia and thiopental-fentanyl-N_2O anesthesia. This is contrary to the results of an in vitro study in which the effects of vecuronium were potentiated (1), but in that study the Cremophor formulation was used. The difference may thus have been due to Cremophor, although it has been proposed that Cremophor may actually have anticholinesterase properties (1).

In the first phase of our study, we assessed the dose-response relationship for vecuronium in humans. There was no significant difference in our final estimates of the ED_{95} for vecuronium with or without propofol, and the values obtained were indeed similar to those previously reported using a similar technique of estimation (6).

In the second phase of the study, we found no difference between the groups in terms of the onset time. Onset of neuromuscular blockade is largely dependent on cardiac output and muscle blood flow to deliver the drug to its receptor site, and the potency, affinity, or diffusion characteristics of the drug are of secondary importance (7). Hence, the lack of any difference in onset time is not surprising. We might have expected a difference only if there was a marked alteration in cardiac output between the two anesthetic techniques used. The subsequent recovery of neuromuscular function occurs as the plasma concentration of vecuronium declines with redistribution and metabolism. Because there was no significant difference between the groups in the time to recovery to 25% of control twitch height, or in the time for spontaneous recovery from 25% to 75% of control, we must conclude that there is no evidence for any significant interaction. We are able to confirm the findings of previous workers with respect to a lack of interaction between the emulsion formulation of propofol and vecuronium (3), although these authors used a cumulative dose-response technique. In addition, they used a relatively small dose of 43 μg/kg of vecuronium to study the onset and duration in contrast to a clinically applicable dose of 80 μg/kg used in the present study. The study of Nightingale et al. (4) is not directly comparable to ours, even though the results were similar. Whereas we used propofol for both induction and maintenance of anesthesia, they assessed the effects of only an induction dose of propofol. Moreover, they examined the effects of only a small single dose of vecuronium that produced approximately 50% block; in addition, they used electromyography for measurement of neuromuscular block.

The original animal studies using the Cremophor preparation led to the suggestion that any interaction was a direct intracellular effect of propofol on the muscle (1) rather than due to the effect of Cremophor, because Cremophor was suggested by these authors to have an anticholinesterase effect. They further speculated that a non-Cremophor preparation may prolong the effect of muscle relaxants even more markedly. However, these explanations are not relevant in the context of the present study, where the emulsion formulation showed no potentiation of the effects of vecuronium. Moreover, the Cremophor preparation is no longer in use. As no interaction has been observed between clinically useful doses of thiopental and vecuronium (8), the possibility that we have masked the action of propofol by the use of thiopental in our control groups seems unlikely.

In conclusion, the emulsion formulation of propofol does not have any significant effect on the neuromuscular blocking properties of vecuronium in humans.

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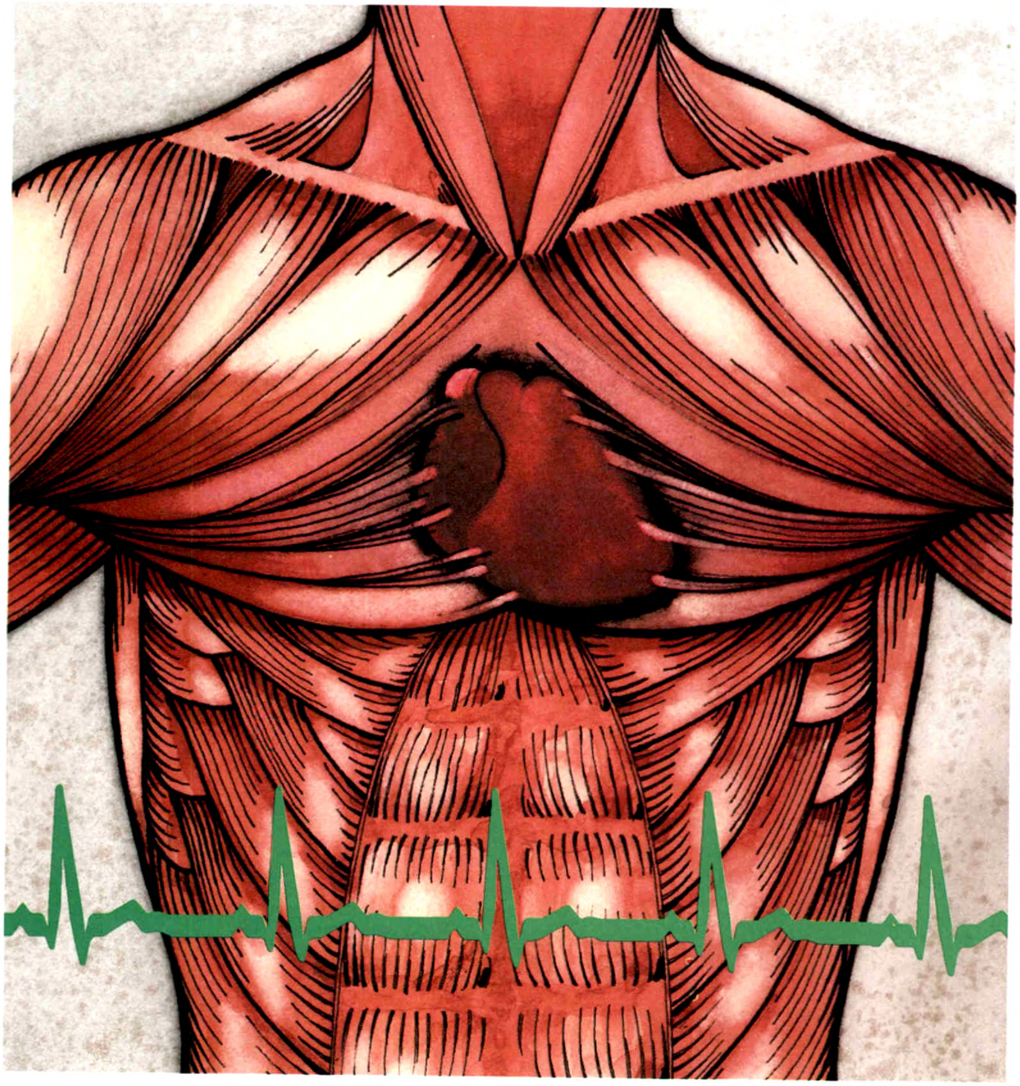

NUROMAX® INJECTION
(doxacurium chloride) 1 mg/mL

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A Long-Acting Neuromuscular Blocker

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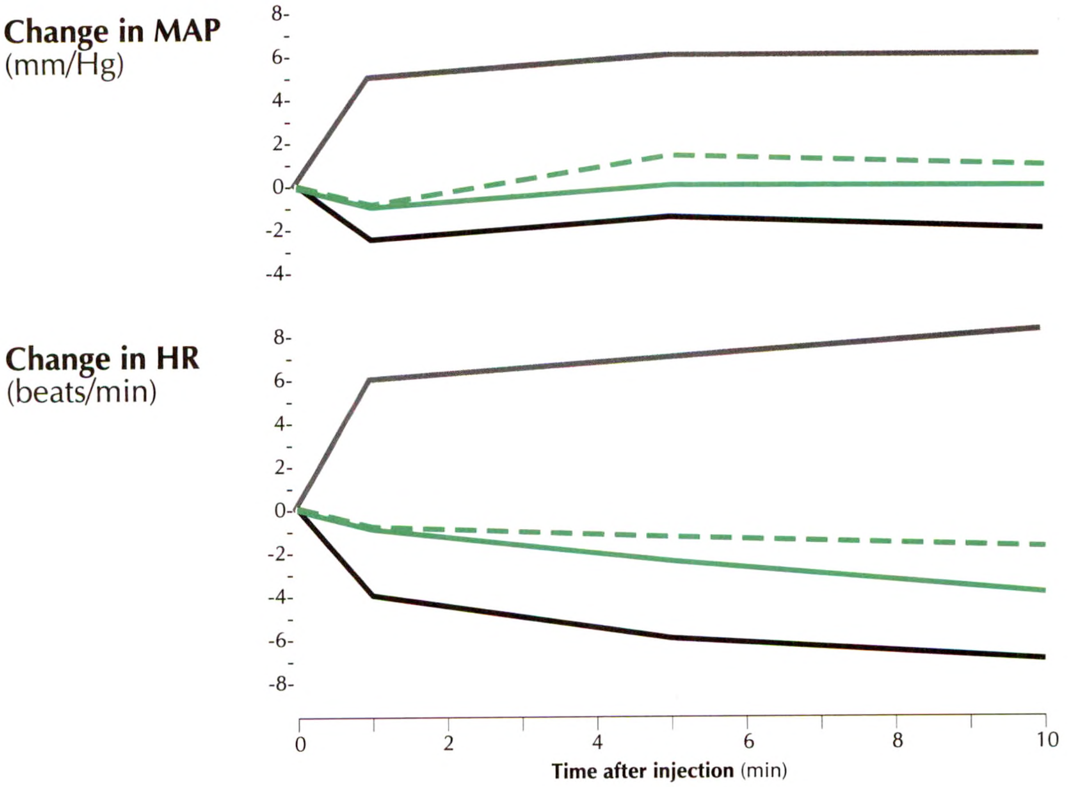
(doxacurium chloride)

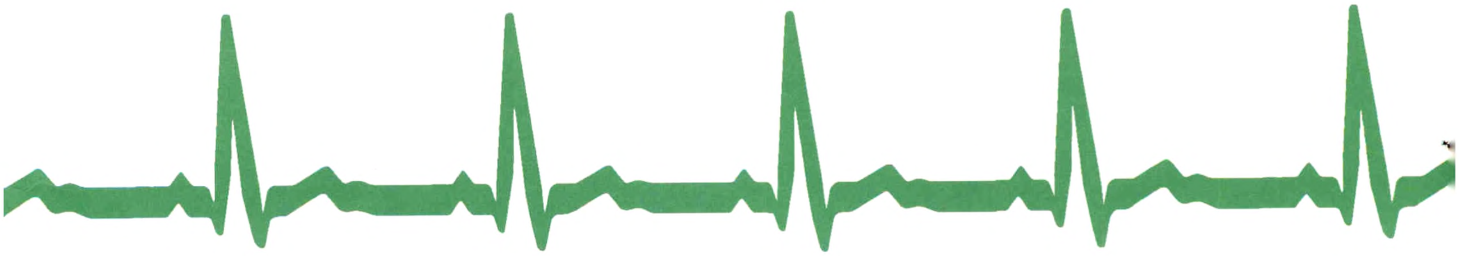
Excellent CV Stability

Cardiovascular stability comparable with vecuronium



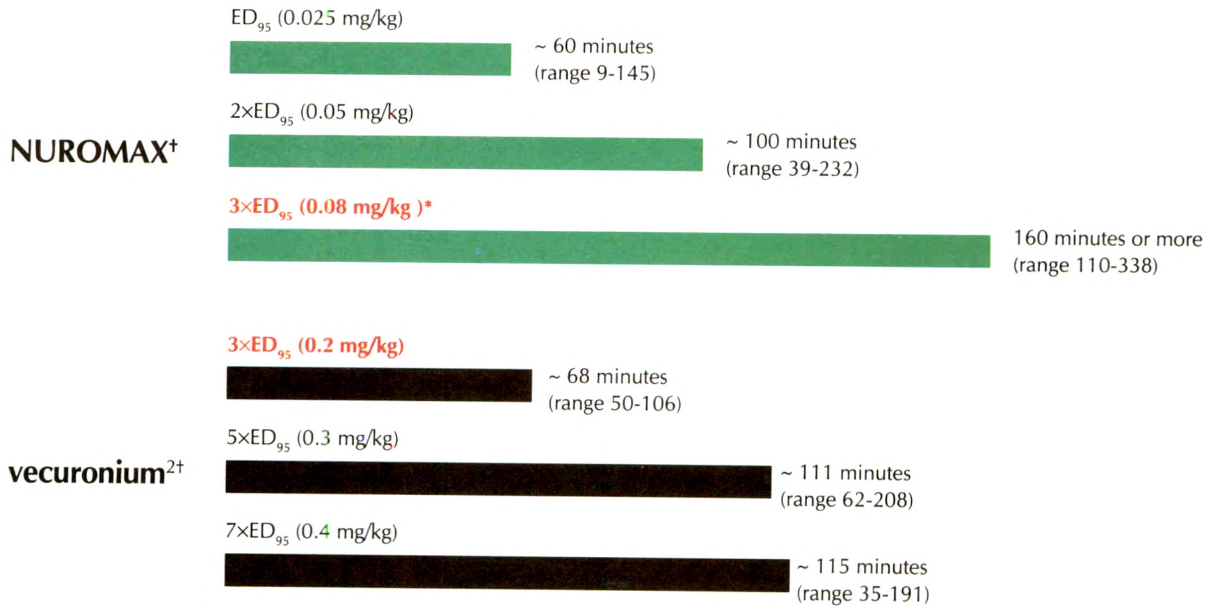
Emmott et al[1] compared the hemodynamic effects of Nuromax 0.037 and 0.075 mg/kg with the effects of pancuronium 0.09 mg/kg and vecuronium 0.075 mg/kg in 36 CABG patients (9 patients, each group).
Mean changes from baseline values of mean systemic arterial pressure (MAP) and heart rate (HR) at 1, 5 and 10 min after administration.
All routine cardiac and vasoactive medications were continued up to the morning of surgery.

- – – doxacurium 0.037 mg/kg
- ─── doxacurium 0.075 mg/kg
- ▨▨▨ pancuronium 0.09 mg/kg
- ━━━ vecuronium 0.075 mg/kg



Longer acting than "high-dose" vecuronium

Clinically effective block (time to 25% recovery)



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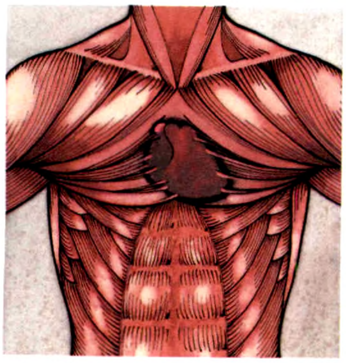
*This dose should be reserved for instances in which a need for very prolonged neuromuscular block is anticipated.

†Numbers shown are not directly comparable since these data have been compiled from different study populations.

- **Cardiovascular stability comparable with normal saline** [3]
- **Noncumulative**
- **Ready-to-use solution**
- **Vials stored at room temperature, no refrigeration required**
- **Supplied as a 5 mL vial, 1 mg/mL**



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NUROMAX® INJECTION
(DOXACURIUM CHLORIDE)

Brief Summary

This drug should be administered only by adequately trained individuals familiar with its actions, characteristics, and hazards.

Individualization of Dosages: In elderly patients or patients who have impaired renal function, the potential for a prolongation of block may be reduced by decreasing the initial Nuromax dose and by titrating the dose to achieve the desired depth of block. In obese patients (patients weighing $\geq$ 30% more than ideal body weight for height), the Nuromax dose should be determined using the patient's ideal body weight (IBW), according to the following formulae:

Men: IBW in kg = [106 + (6 x inches in height above 5 feet)]/2.2
Women: IBW in kg = [100 + (5 x inches in height above 5 feet)]/2.2

Dosage requirements for patients with severe liver disease are variable; some patients may require a higher than normal initial Nuromax dose to achieve clinically effective block. Once adequate block is established, the clinical duration of block may be prolonged in such patients relative to patients with normal liver function.

As with pancuronium, metocurine, and vecuronium, resistance to Nuromax, manifested by a reduced intensity and/or shortened duration of block, must be considered when Nuromax is selected for use in patients receiving phenytoin or carbamazepine (see **Drug Interactions** subsection of PRECAUTIONS).

As with other nondepolarizing neuromuscular blocking agents, a reduction in dosage of Nuromax must be considered in cachectic or debilitated patients, in patients with neuromuscular diseases, severe electrolyte abnormalities, or carcinomatosis, and in other patients in whom potentiation of neuromuscular block or difficulty with reversal is anticipated. Increased doses of Nuromax may be required in burn patients (see PRECAUTIONS).

INDICATIONS AND USAGE: Nuromax is a long-acting neuromuscular blocking agent, indicated as an adjunct to general anesthesia, to provide skeletal muscle relaxation during surgery. Nuromax can also be used to provide skeletal muscle relaxation for endotracheal intubation.

CONTRAINDICATIONS: Nuromax is contraindicated in patients known to have hypersensitivity to it.

WARNINGS: NUROMAX SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH THE DRUG'S ACTIONS AND THE POSSIBLE COMPLICATIONS OF ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND AN ANTAGONIST ARE WITHIN IMMEDIATE REACH. IT IS RECOMMENDED THAT CLINICIANS ADMINISTERING LONG-ACTING NEUROMUSCULAR BLOCKING AGENTS SUCH AS NUROMAX EMPLOY A PERIPHERAL NERVE STIMULATOR TO MONITOR DRUG RESPONSE, NEED FOR ADDITIONAL RELAXANTS, AND ADEQUACY OF SPONTANEOUS RECOVERY OR ANTAGONISM.

NUROMAX HAS NO KNOWN EFFECT ON CONSCIOUSNESS, PAIN THRESHOLD, OR CEREBRATION. TO AVOID DISTRESS TO THE PATIENT, NEUROMUSCULAR BLOCK SHOULD NOT BE INDUCED BEFORE UNCONSCIOUSNESS.

Nuromax Injection is acidic (pH 3.9 to 5.0) and may not be compatible with alkaline solutions having a pH greater than 8.5 (*e.g.*, barbiturate solutions).

Nuromax Injection contains benzyl alcohol. In newborn infants, benzyl alcohol has been associated with an increased incidence of neurological and other complications which are sometimes fatal. See **Pediatric Use** subsection of PRECAUTIONS.

PRECAUTIONS: General: Nuromax has no clinically significant effects on heart rate; therefore, Nuromax will not counteract the bradycardia produced by many anesthetic agents or by vagal stimulation. Neuromuscular blocking agents may have a profound effect in patients with neuromuscular diseases (*e.g.*, myasthenia gravis and the myasthenic syndrome). In these and other conditions in which prolonged neuromuscular block is a possibility (*e.g.*, carcinomatosis), the use of a peripheral nerve stimulator and a small test dose of Nuromax is recommended to assess the level of neuromuscular block and to monitor dosage requirements. Shorter acting muscle relaxants than Nuromax may be more suitable for these patients.

Resistance to nondepolarizing neuromuscular blocking agents may develop in patients with burns depending upon the time elapsed since the injury and the size of the burn. Nuromax has not been studied in patients with burns. Acid-base and/or serum electrolyte abnormalities may potentiate or antagonize the action of neuromuscular blocking agents. The action of neuromuscular blocking agents may be enhanced by magnesium salts administered for the management of toxemia of pregnancy. Nuromax has not been studied in patients with asthma. No data are available to support the use of Nuromax by intramuscular injection. **Renal and Hepatic Disease:** Nuromax has been studied in patients with end-stage kidney (n=8) or liver (n=7) disease undergoing transplantation procedures (see CLINICAL PHARMACOLOGY). The possibility of prolonged neuromuscular block in patients undergoing renal transplantation and the possibility of a variable onset and duration of neuromuscular block in patients undergoing liver transplantation must be considered when Nuromax is used in such patients. **Obesity:** Administration of Nuromax on the basis of actual body weight is associated with a prolonged duration of action in obese patients (patients weighing $\geq$ 30% more than ideal body weight for height) (see CLINICAL PHARMACOLOGY). Therefore, the dose of Nuromax should be based upon ideal body weight in obese patients (see **Individualization of Dosages** subsection of CLINICAL PHARMACOLOGY). **Malignant Hyperthermia (MH):** In a study of MH-susceptible pigs, Nuromax did not trigger MH. Nuromax has not been studied in MH-susceptible patients. Since MH can develop in the absence of established triggering agents, the clinician should be prepared to recognize and treat MH in any patient scheduled for general anesthesia. **Long-Term Use in the Intensive Care Unit (ICU):** No data are available on the long-term use of Nuromax in patients undergoing mechanical ventilation in the ICU. **Drug Interactions:** Prior administration of succinylcholine has no clinically important effect on the neuromuscular blocking action of Nuromax. The use of Nuromax before succinylcholine to attenuate some of the side effects of succinylcholine has not been studied. There are no clinical data on concomitant use of Nuromax and other nondepolarizing neuromuscular blocking agents. Isoflurane, enflurane and halothane decrease the ED_{50} of Nuromax by 30% to 45%. These agents may also prolong the clinically effective duration of action by up to 25%. Other drugs which may enhance the neuromuscular blocking action of nondepolarizing agents such as Nuromax include certain antibiotics (*e.g.*, aminoglycosides, tetracyclines, bacitracin, polymyxins, lincomycin, clindamycin, colistin, and sodium colistimethate), magnesium salts, lithium, local anesthetics, procainamide, and quinidine. As with some other nondepolarizing neuromuscular blocking agents, the time of onset of neuromuscular block induced by Nuromax is lengthened and the duration of block is shortened in patients receiving phenytoin or carbamazepine. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Carcinogenesis and fertility studies have not been performed. Nuromax was evaluated in a battery of four short-term mutagenicity tests. It was non-mutagenic in the Ames Salmonella assay, in the mouse lymphoma assay, and in the human lymphocyte assay. In the *in vivo* rat bone marrow cytogenetic assay, statistically significant increases in the incidence of structural abnormalities, relative to vehicle controls, were observed in male rats dosed with 0.1 mg/kg (0.625 mg/m^2) Nuromax and sacrificed at 6 hours, but not at 24 or 48 hours, and in female rats dosed with 0.2 mg/kg (1.25 mg/m^2) Nuromax and sacrificed at 24 hours, but not at 6 or 48 hours. There was no increase in structural abnormalities in either male or female rats given 0.3 mg/kg (1.875 mg/m^2) Nuromax and sacrificed at 6, 24, or 48 hours. Thus, the incidence of abnormalities in the *in vivo* rat bone marrow cytogenetic assay was not dose-dependent and, therefore, the likelihood that the observed abnormalities were treatment-related or clinically significant is low. **Pregnancy:** Teratogenic Effects: Pregnancy Category C. Teratology testing in nonventilated, pregnant rats and mice treated subcutaneously with maximum subparalyzing doses of Nuromax revealed no maternal or fetal toxicity or teratogenic effects. There are no adequate and well-controlled studies of Nuromax in pregnant women. Because animal studies are not always predictive of human response and the doses used were subparalyzing, Nuromax should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Labor and Delivery:** The use of Nuromax during labor, vaginal delivery, or cesarean section has not been studied. It is not known whether Nuromax administered to the mother has immediate or delayed effects on the fetus. The duration of action of Nuromax exceeds the usual duration of operative obstetrics (cesarean section). Therefore, Nuromax is not recommended for use in patients undergoing C-section. **Nursing Mothers:** It is not known whether Nuromax is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised following Nuromax administration to a nursing woman. **Pediatric Use:** Nuromax has not been studied in children below the age of 2 years. See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION for clinical experience and recommendations for use in children 2 to 12 years of age. **Geriatric Use:** Nuromax has been used in elderly patients, including patients with significant cardiovascular disease. In elderly patients the onset of maximum block is slower and the duration of neuromuscular block produced by Nuromax is more variable and, in some cases, longer than in young adult patients (see **Pharmacodynamics** and **Individualization of Dosages** subsections of CLINICAL PHARMACOLOGY).

ADVERSE REACTIONS: The most frequent adverse effect of nondepolarizing blocking agents as a class consists of an extension of the pharmacological action beyond the time needed for surgery and anesthesia. This effect may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiratory insufficiency and apnea which require manual or mechanical ventilation until recovery is judged to be clinically adequate (see OVERDOSAGE). Inadequate reversal of neuromuscular block from Nuromax is possible, as with all nondepolarizing agents. Prolonged neuromuscular block and inadequate reversal may lead to postoperative complications. **Observed in Clinical Trials:** Adverse experiences were uncommon among the 1034 surgical patients and volunteers who received Nuromax and other drugs in U.S. clinical studies in the course of a wide variety of procedures conducted during balanced or inhalational anesthesia. The following adverse experiences were reported in patients administered Nuromax (all events judged by investigators during the clinical trials to have a possible causal relationship):

Incidence Greater than 1% - None

Incidence Less than 1% -

Cardiovascular[*]:	hypotension,[†] flushing,[†] ventricular fibrillation, myocardial infarction
Respiratory:	bronchospasm, wheezing
Dermatological:	urticaria, injection site reaction
Special Senses:	diplopia
Nonspecific:	difficult neuromuscular block reversal, prolonged drug effect, fever

[*] Reports of ventricular fibrillation (n=1) and myocardial infarction (n=1) were limited to ASA Class 3-4 patients undergoing cardiac surgery (n=142).

[†] 0.3% incidence. All other reactions unmarked were $\leq$ 0.1%.

OVERDOSAGE: Overdosage with neuromuscular blocking agents may result in neuromuscular block beyond the time needed for surgery and anesthesia. The primary treatment is maintenance of a patent airway and controlled ventilation until recovery of normal neuromuscular function is assured. Once evidence of recovery from neuromuscular block is observed, further recovery may be facilitated by administration of an anticholinesterase agent (*e.g.*, neostigmine, edrophonium) in conjunction with an appropriate anticholinergic agent (see **Antagonism of Neuromuscular Block**).

Antagonism of Neuromuscular Block: ANTAGONISTS (SUCH AS NEOSTIGMINE) SHOULD NOT BE ADMINISTERED PRIOR TO THE DEMONSTRATION OF SOME SPONTANEOUS RECOVERY FROM NEUROMUSCULAR BLOCK. THE USE OF A NERVE STIMULATOR TO DOCUMENT RECOVERY AND ANTAGONISM OF NEUROMUSCULAR BLOCK IS RECOMMENDED. T_4/T_1 SHOULD BE > ZERO BEFORE ANTAGONISM IS ATTEMPTED.

In an analysis of patients in whom antagonism of neuromuscular block was evaluated following administration of single doses of neostigmine averaging 0.06 mg/kg (range: 0.05 to 0.075) administered at approximately 25% T_1 spontaneous recovery during balanced anesthesia, 71% of patients exhibited $T_4/T_1 \geq 0.7$ before monitoring was discontinued. For these patients, the mean time to $T_4/T_1 \geq 0.7$ was 19 minutes (range: 7 to 55). As with other long-acting nondepolarizing neuromuscular blocking agents, the time for recovery of neuromuscular function following administration of neostigmine is dependent upon the level of residual neuromuscular block at the time of attempted reversal; longer recovery times than those cited above may be anticipated when neostigmine is administered at more profound levels of block (*i.e.*, at < 25% T_1 recovery).

Patients should be evaluated for adequate clinical evidence of antagonism, *e.g.*, 5-second head lift, and grip strength. Ventilation must be supported until no longer required. As with other neuromuscular blocking agents, physicians should be alert to the possibility that the action of the drugs used to antagonize neuromuscular block may wear off before the effects of Nuromax on the neuromuscular junction have declined sufficiently.

Antagonism may be delayed in the presence of debilitation, carcinomatosis, and the concomitant use of certain broad spectrum antibiotics, or anesthetic agents and other drugs which enhance neuromuscular block or separately cause respiratory depression (see **Drug Interactions** subsection of PRECAUTIONS). Under such circumstances the management is the same as that of prolonged neuromuscular block.

In clinical trials, a dose of 1 mg/kg edrophonium was not as effective as a dose of 0.06 mg/kg neostigmine in antagonizing moderate to deep levels of neuromuscular block (i.e., < 60% T_1 recovery). Therefore, the use of 1 mg/kg edrophonium is not recommended for reversal from moderate to deep levels of block. The use of pyridostigmine has not been studied.

Adults: *Initial Doses:* When administered as a component of a thiopental/narcotic induction-intubation paradigm as well as for production of long-duration neuromuscular block during surgery, 0.05 mg/kg (2 x ED_{95}) Nuromax produces good-to-excellent conditions for tracheal intubation in 5 minutes in approximately 90% of patients. Lower doses of Nuromax may result in a longer time for development of satisfactory intubation conditions. Clinically effective neuromuscular block may be expected to last approximately 100 minutes on average (range: 39 to 232) following 0.05 mg/kg Nuromax administered to patients receiving balanced anesthesia.

An initial Nuromax dose of 0.08 mg/kg (3 x ED_{95}) should be reserved for instances in which a need for very prolonged neuromuscular block is anticipated. In approximately 90% of patients, good-to-excellent intubation conditions may be expected in 4 minutes after this dose; however, clinically effective block may be expected to persist for as long as 160 minutes or more (range: 110 to 338) (see CLINICAL PHARMACOLOGY).

STORAGE: Store Nuromax Injection at room temperature of 15° to 25°C (59° to 77°F). DO NOT FREEZE.

U.S. Patent No. 4701460

March 1991 562004

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2. Tullock WC, Diana P, Cook R, et al. Neuromuscular and cardiovascular effects of high-dose vecuronium. *Anesth Analg*. 1990;70:86-90.
3. Stoops CM, Curtis CA, Kovach DA, et al. Hemodynamic effects of doxacurium chloride in patients receiving oxygen sufentanil anesthesia for coronary artery bypass grafting or valve replacement. *Anesthesiology*. 1988;69:365-370.

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THE ADVANTAGE OF CO-INDUCTION

Anesthetic Synergy

VERSED first, followed by a second anesthetic

When given first, a small dose of VERSED® (midazolam HCl/Roche) may lower the induction ED_{50} of barbiturates or narcotics up to 75%.[1-4] This synergistic effect appears o result from a mutual enhancement of binding-site affinity.[1-3] Clinically, co-induction may decrease toxicity and speed recovery.[2] VERSED can also abolish the excitatory effects and emergence phenomena associated with some induction agents,[5] and its potent amnestic effect may avoid breakthrough awareness at times when short-acting induction agents may be wearing off.

- **Allows lower doses of induction agents[1-5]**
- **A smooth induction[5]**
- **Less risk of breakthrough awareness[5]**
- **A smooth emergence[5]**

Dosing considerations

When VERSED is used before other intravenous agents for induction of anesthesia, the initial dose of each agent may be significantly reduced, at times to as low as 25% of the usual initial dose of the individual agents.

As a standard precaution, prior to I.V. administration of VERSED in any dose, oxygen and resuscitative equipment should be immediately available. VERSED should be used as an induction agent only by persons trained in anesthesiology and who are familiar with all dosing and administration guidelines. Reduce dosage in elderly or debilitated patients, in patients receiving narcotic premedication and in those with limited pulmonary reserve.

It is recommended that patients do not drive or operate hazardous machinery after receiving VERSED until the effects of the drug (*e.g.,* drowsiness) are gone or until the day after anesthesia, whichever is longer. The decision must be individualized.

Please see summary of product information on following page.

INJECTABLE

VERSED®

midazolam HCl/Roche Ⓒⅳ

FIRST

Injectable VERSED is available in 1 mg/mL and 5 mg/mL strengths.

References: 1. Tverskoy M, et al. Midazolam-thiopental anesthetic interaction in patients. *Anesth Analg*. 1988;67:342-345. **2.** Vinik HR, Bradley EL Jr, Kissin I. Midazolam for coinduction of thiopental anesthesia in patients. *Anesthesiology*. 1990; 73(3A):A1216. **3.** Vinik HR, Bradley EL Jr, Kissin I. Midazolam-alfentanil synergism for anesthetic induction in patients. *Anesth Analg*. 1989;69:213-217. **4.** Ben-Shlomo I, et al. Midazolam acts synergistically with fentanyl for induction of anaesthesia. *Br J Anaesth*. 1990;64:45-47. **5.** White PF. Comparative evaluation of intravenous agents for rapid sequence induction — thiopental, ketamine, and midazolam. *Anesthesiology*. 1982;57:279-284.

VERSED®
midazolam HCl/Roche ℞
INJECTION

Before prescribing, please consult complete product information, a summary of which follows:

> Intravenous VERSED has been associated with respiratory depression and respiratory arrest, especially when used for conscious sedation. In some cases, where this was not recognized promptly and treated effectively, death or hypoxic encephalopathy has resulted. Intravenous VERSED should be used only in hospital or ambulatory care settings, including physicians' offices, that provide for continuous monitoring of respiratory and cardiac function. Immediate availability of resuscitative drugs and equipment and personnel trained in their use should be assured. (See WARNINGS.)
> The initial intravenous dose for conscious sedation may be as little as 1 mg, but should not exceed 2.5 mg in a normal healthy adult. Lower doses are necessary for older (over 60 years) or debilitated patients and in patients receiving concomitant narcotics or other CNS depressants. The initial dose and all subsequent doses should never be given as a bolus; administer over at least 2 minutes and allow an additional 2 or more minutes to fully evaluate the sedative effect. The use of the 1 mg/mL formulation or dilution of the 1 mg/mL or 5 mg/mL formulation is recommended to facilitate slower injection. Consult complete product information under DOSAGE AND ADMINISTRATION for complete dosing information.

CONTRAINDICATIONS: Patients with known hypersensitivity to the drug. Benzodiazepines are contraindicated in patients with acute narrow angle glaucoma; may be used in open angle glaucoma only if patients are receiving appropriate therapy.

Not intended for intrathecal or epidural administration due to the presence of the preservative benzyl alcohol.

WARNINGS: Never use without individualization of dosage. Prior to IV use in any dose, ensure immediate availability of oxygen, resuscitative equipment and skilled personnel for maintenance of a patent airway and support of ventilation. Continuously monitor for early signs of underventilation or apnea, which can lead to hypoxia/cardiac arrest unless effective countermeasures are taken immediately. Vital signs should continue to be monitored during the recovery period.

Because IV VERSED depresses respiration, and opioid agonists and other sedatives can add to this depression, it should be administered as an induction agent only by a person trained in general anesthesia and should be used for conscious sedation only in the presence of personnel skilled in early detection of underventilation, maintaining a patent airway and supporting ventilation. **For conscious sedation, do not administer IV by rapid or single bolus.** Serious cardiorespiratory adverse events have occurred. These have included respiratory depression, apnea, respiratory arrest and/or cardiac arrest, sometimes resulting in death. There have been rare reports of hypotensive episodes requiring treatment during or after diagnostic or surgical manipulations in patients who have received VERSED. Hypotension occurred more frequently in the conscious sedation studies in patients premedicated with narcotic.

Reactions such as agitation, involuntary movements, hyperactivity and combativeness have been reported. These may be due to inadequate or excessive dosing or improper administration; however, the possibility of cerebral hypoxia or true paradoxical reactions should be considered. Should these reactions occur, response to each dose of VERSED and all other drugs should be evaluated before proceeding.

Concomitant use of barbiturates, alcohol or other CNS depressants may increase the risk of underventilation or apnea and may contribute to profound and/or prolonged drug effect. Narcotic premedication also depresses the ventilatory response to carbon dioxide stimulation.

Higher risk surgical, elderly or debilitated patients require lower dosages for induction of anesthesia, premedicated or not. Patients with chronic obstructive pulmonary disease are unusually sensitive to the respiratory depressant effect of VERSED. Patients with chronic renal failure and patients with congestive heart failure eliminate midazolam more slowly. Because elderly patients frequently have inefficient function of one or more organ systems, and because dosage requirements have been shown to decrease with age, reduce initial dosage and consider possibility of a profound and/or prolonged effect.

Do not administer in shock, coma, acute alcohol intoxication with depression of vital signs. Particular care should be exercised in the use of IV VERSED in patients with uncompensated acute illnesses, such as severe fluid or electrolyte disturbances.

Guard against unintended intra-arterial injection; hazards in humans unknown. Avoid extravasation.

VERSED should only be administered IM or IV. Safety and efficacy of other routes of administration are not established.

Gross tests of recovery from the effects of VERSED cannot alone predict reaction time under stress. This drug is never used alone during anesthesia, and the contribution of other perioperative drugs and events can vary. The decision as to when patients may engage in activities requiring mental alertness must be individualized; it is recommended that no patient should operate hazardous machinery or a motor vehicle until the effects of the drug, such as drowsiness, have subsided or until the day after anesthesia, whichever is longer.

Usage in Pregnancy: An increased risk of congenital malformations associated with the use of benzodiazepines (diazepam and chlordiazepoxide) has been suggested in several studies. If VERSED is used during pregnancy, apprise the patient of the potential hazard to the fetus.

PRECAUTIONS: *General:* Decrease intravenous doses in elderly and debilitated patients. These patients will also probably take longer to recover completely after VERSED for induction of anesthesia.

VERSED does not protect against increased intracranial pressure or against the heart rate rise and/or blood pressure rise associated with endotracheal intubation under light general anesthesia.

Information for patients: Communicate the following information and instructions to the patient when appropriate: 1. Inform your physician about any alcohol consumption and medicine you are now taking, including nonprescription drugs. Alcohol has an increased effect when consumed with benzodiazepines; therefore, caution should be exercised regarding simultaneous ingestion of alcohol and benzodiazepines. 2. Inform your physician if you are pregnant or are planning to become pregnant. 3. Inform your physician if you are nursing.

Drug Interactions: The sedative effect of IV VERSED is accentuated by premedication, particularly narcotics (*e.g.*, morphine, meperidine, fentanyl) and also secobarbital and Innovar (fentanyl and droperidol). Consequently, adjust the dosage according to the type and amount of premedication.

A moderate reduction in induction dosage requirements of thiopental (about 15%) has been noted following use of IM VERSED for premedication.

IV administration of VERSED decreases the minimum alveolar concentration (MAC) of halothane required for general anesthesia. This decrease correlates with the dose of VERSED administered.

Although the possibility of minor interactive effects has not been fully studied, VERSED and pancuronium have been used together in patients without noting clinically significant changes in dosage, onset or duration. VERSED does not protect against the characteristic circulatory changes noted after administration of succinylcholine or pancuronium, or against the increased intracranial pressure noted following administration of succinylcholine. VERSED does not cause a clinically significant change in dosage, onset or duration of a single intubating dose of succinylcholine.

No significant adverse interactions with commonly used premedications or drugs used during anesthesia and surgery (including atropine, scopolamine, glycopyrrolate, diazepam, hydroxyzine, d-tubocurarine, succinylcholine and nondepolarizing muscle relaxants) or topical local anesthetics (including lidocaine, dyclonine HCl and Cetacaine) have been observed.

Clearance of midazolam and certain other benzodiazepines may be delayed with concomitant administration of cimetidine (but not ranitidine). Clinical significance of this interaction is unclear.

Drug/laboratory test interactions: Midazolam has not been shown to interfere with clinical laboratory test results.

Carcinogenesis, mutagenesis, impairment of fertility: Midazolam maleate was administered to mice and rats for two years. At the highest dose (80 mg/kg/day) female mice had a marked increase in incidence of hepatic tumors and male rats had a small but significant increase in benign thyroid follicular cell tumors. These tumors were found after chronic use, whereas human use will ordinarily be of single or several doses.

Midazolam did not have mutagenic activity in tests that were conducted.

A reproduction study in rats did not show any impairment of fertility at up to ten times the human IV dose.

Pregnancy: Teratogenic effects: Pregnancy Category D. See WARNINGS section.

Midazolam maleate injectable, at 5 and 10 times the human dose, did not show evidence of teratogenicity in rabbits and rats.

Labor and delivery: Use in obstetrics has not been evaluated. Because midazolam is transferred transplacentally and because other benzodiazepines given in the last weeks of pregnancy have resulted in neonatal CNS depression, VERSED is not recommended for obstetrical use.

Nursing mothers: Excreted in human milk. Not recommended for use in nursing mothers.

Pediatric use: Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS: See WARNINGS concerning serious cardiorespiratory events and possible paradoxical reactions. Fluctuations in vital signs following parenteral administration were the most frequently seen findings and included decreased tidal volume and/or respiratory rate decrease (23.3% of patients following IV and 10.8% of patients following IM administration) and apnea (15.4% of patients following IV administration), as well as variations in blood pressure and pulse rate.

Following IM injection: headache (1.3%); local effects at IM site: pain (3.7%), induration (0.5%), redness (0.5%), muscle stiffness (0.3%).

IM administration to elderly and/or high-risk surgical patients has been associated with rare reports of death under circumstances compatible with cardiorespiratory depression. In most of these cases, patients also received other CNS depressants capable of depressing respiration, especially narcotics.

Following IV administration: hiccoughs (3.9%), nausea (2.8%), vomiting (2.6%), coughing (1.3%), "oversedation" (1.6%), headache (1.5%), drowsiness (1.2%); local effects at the IV site: tenderness (5.6%), pain during injection (5.0%), redness (2.6%), induration (1.7%), phlebitis (0.4%). Other effects (<1%) mainly following IV administration: *Respiratory:* Laryngospasm, bronchospasm, dyspnea, hyperventilation, wheezing, shallow respirations, airway obstruction, tachypnea. *Cardiovascular:* Bigeminy, premature ventricular contractions, vasovagal episode, bradycardia, tachycardia, nodal rhythm. *Gastrointestinal:* Acid taste, excessive salivation, retching. *CNS/Neuromuscular:* Retrograde amnesia, euphoria, hallucination, confusion, argumentativeness, nervousness, anxiety, grogginess, restlessness, emergence delirium or agitation, prolonged emergence from anesthesia, dreaming during emergence, sleep disturbance, insomnia, nightmares, athetoid movements, seizure-like activity, ataxia, dizziness, dysphoria, slurred speech, dysphonia, paresthesia. *Special Sense:* Blurred vision, diplopia, nystagmus, pinpoint pupils, cyclic movements of eyelids, visual disturbance, difficulty focusing eyes, ears blocked, loss of balance, lightheadedness. *Integumentary:* Hive-like elevation at injection site, swelling or feeling of burning, warmth or coldness at injection site. *Hypersensitivity:* Allergic reactions, including anaphylactoid reactions, hives, rash, pruritus. *Miscellaneous:* Yawning, lethargy, chills, weakness, toothache, faint feeling, hematoma.

Drug Abuse and Dependence: Available data concerning the drug abuse and dependence potential of midazolam suggest that its abuse potential is at least equivalent to that of diazepam.

OVERDOSAGE: Manifestations would resemble those observed with other benzodiazepines (*e.g.*, sedation, somnolence, confusion, impaired coordination, diminished reflexes, coma, untoward effects on vital signs). No specific organ toxicity would be expected.

DOSAGE AND ADMINISTRATION: VERSED is a potent sedative agent which requires slow administration and individualization of dosage. Clinical experience has shown VERSED to be 3 to 4 times as potent per mg as diazepam. BECAUSE SERIOUS AND LIFE-THREATENING CARDIORESPIRATORY ADVERSE EVENTS HAVE BEEN REPORTED, PROVISION FOR MONITORING, DETECTION AND CORRECTION OF THESE REACTIONS MUST BE MADE FOR EVERY PATIENT TO WHOM VERSED INJECTION IS ADMINISTERED, REGARDLESS OF AGE OR HEALTH STATUS. Excess doses or rapid or single bolus intravenous administration may result in respiratory depression and/or arrest. (See WARNINGS.) Prior to use refer to the DOSAGE AND ADMINISTRATION section in the complete product information.

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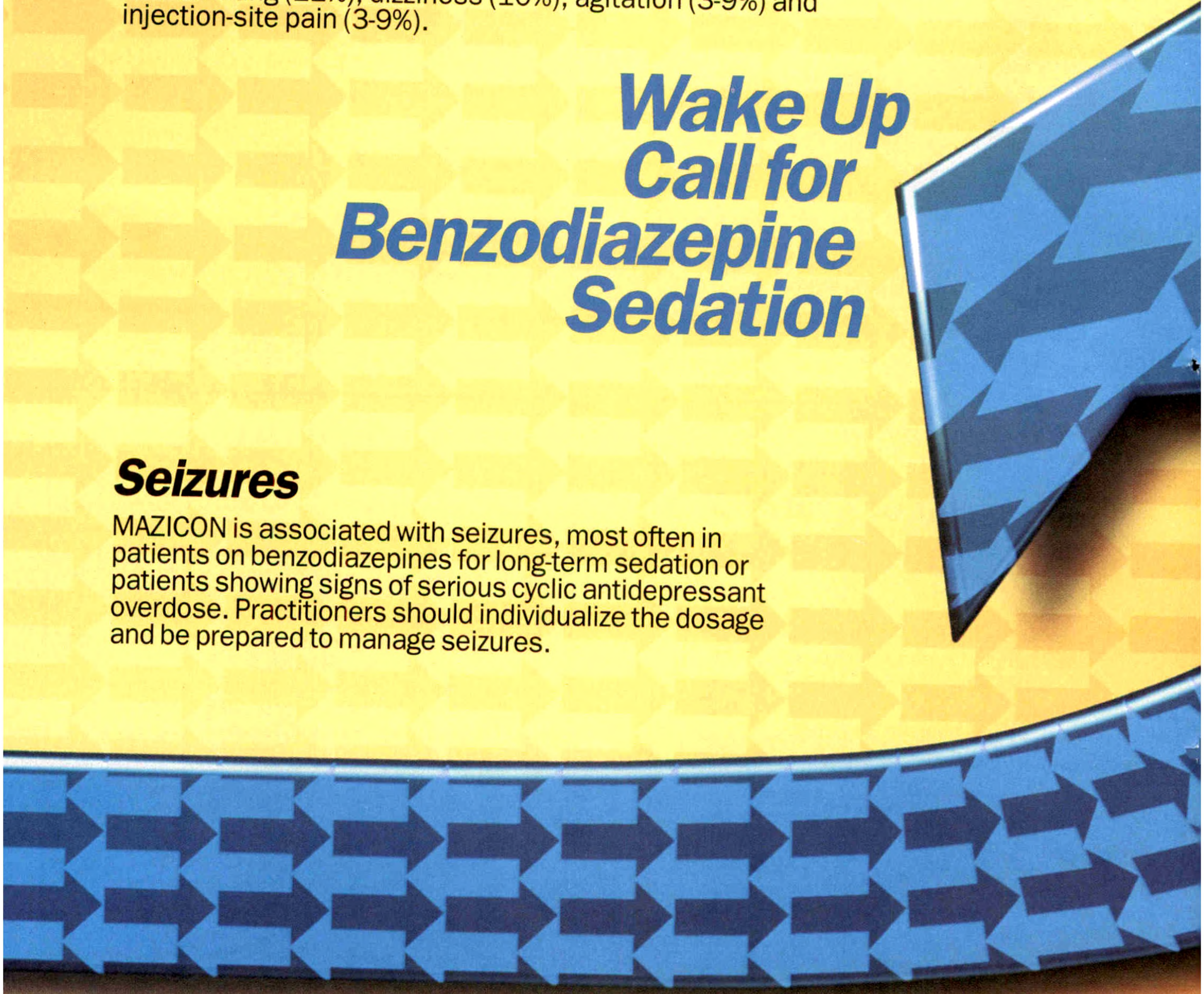
A specific reversal agent for benzodiazepine sedation

- MAZICON (flumazenil/Roche) rapidly and specifically reverses sedation produced by any benzodiazepine
- Promptly restores patients to consciousness—often within minutes of reaching an effective dose
- Reverses benzodiazepine sedative effects only—not the effects of narcotics or other CNS agents

Adverse effects

The most common side effects in clinical trials were nausea and vomiting (11%), dizziness (10%), agitation (3-9%) and injection-site pain (3-9%).

Wake Up Call for Benzodiazepine Sedation



Seizures

MAZICON is associated with seizures, most often in patients on benzodiazepines for long-term sedation or patients showing signs of serious cyclic antidepressant overdose. Practitioners should individualize the dosage and be prepared to manage seizures.

ROCHE®

Please see complete product information on following pages.

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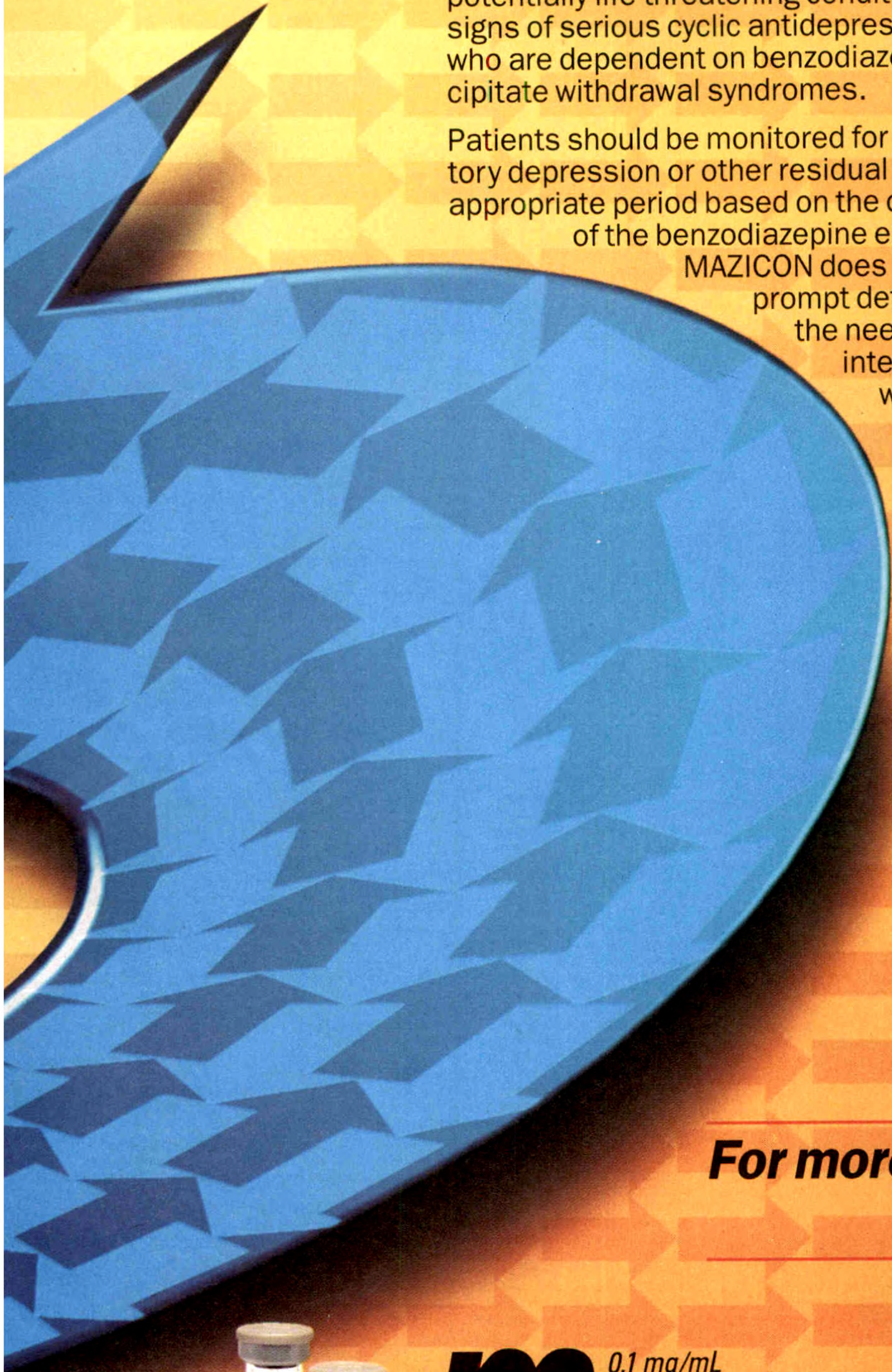
Important safety information

Contraindicated in hypersensitivity to benzodiazepines or MAZICON; in patients taking benzodiazepines for control of potentially life-threatening conditions; and in patients showing signs of serious cyclic antidepressant overdose. In patients who are dependent on benzodiazepines, MAZICON may precipitate withdrawal syndromes.

Patients should be monitored for possible resedation, respiratory depression or other residual benzodiazepine effects for an appropriate period based on the dose and duration of effect of the benzodiazepine employed. The availability of MAZICON does not diminish the need for prompt detection of hypoventilation and the need to be prepared to effectively intervene by establishing an airway and assisting ventilation. MAZICON has not been established as an effective treatment for benzodiazepine-induced hypoventilation.



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Available in
5-mL and
10-mL vials.

0.1 mg/mL
Mazicon I.V. TM
flumazenil/Roche

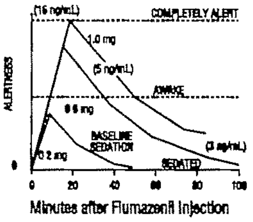
The reversal agent you've been waiting for

MAZICON™
(flumazenil/Roche)
INJECTION

DESCRIPTION: MAZICON™ (flumazenil/Roche) is a benzodiazepine receptor antagonist. Chemically, flumazenil is ethyl 8-fluoro-5,6-dihydro-5-methyl-6-oxo-4H-imidazo[1,5-a](1,4) benzodiazepine-3-carboxylate. Flumazenil has an imidazobenzodiazepine structure, a calculated molecular weight of 303.3.
Flumazenil is a white to off-white crystalline compound with an octanol:buffer partition coefficient of 14 to 1 at pH 7.4. It is insoluble in water but slightly soluble in acidic aqueous solutions. MAZICON is available as a sterile parenteral dosage form for intravenous administration. Each mL contains 0.1 mg of flumazenil compounded with 1.8 mg of methylparaben, 0.2 mg of propylparaben, 0.9% sodium chloride, 0.01% edetate disodium, and 0.01% acetic acid; the pH is adjusted to approximately 4 with hydrochloric acid and/or, if necessary, sodium hydroxide.

CLINICAL PHARMACOLOGY: Flumazenil, an imidazobenzodiazepine derivative, antagonizes the actions of benzodiazepines on the central nervous system. Flumazenil competitively inhibits the activity at the benzodiazepine recognition site on the GABA/benzodiazepine receptor complex. Flumazenil is a weak partial agonist in some animal models of activity, but has little or no agonist activity in man.
Flumazenil does not antagonize the central nervous system effects of drugs affecting GABA-ergic neurons by means other than the benzodiazepine receptor (including ethanol, barbiturates, or general anesthetics) and does not reverse the effects of opioids.
PHARMACODYNAMICS: Intravenous MAZICON has been shown to antagonize sedation, impairment of recall and psychomotor impairment produced by benzodiazepines in healthy human volunteers.
The duration and degree of reversal of benzodiazepine effects are related to the dose and plasma concentrations of flumazenil as shown in the following data from a study in normal volunteers.

Magnitude and Duration of Reversal of Sedation as a Function of Flumazenil Dose*
Flumazenil doses of 0.2, 0.6 & 1.0 mg
(blood level in ng/mL)



*Sedation produced by midazolam infusion at a rate of 0.06 - 0.20 mg/kg/hr in healthy volunteers

Generally, doses of approximately 0.1 to 0.2 mg (corresponding to peak plasma levels of 3 to 6 ng/mL) produce partial antagonism, whereas higher doses of 0.4 to 1.0 mg (peak plasma levels of 12 to 28 ng/mL) usually produce complete antagonism in patients who have received the usual sedating doses of benzodiazepines. The onset of reversal is usually evident within 1 to 2 minutes after the injection is completed. Eighty percent response will be reached within 3 minutes, with the peak effect occurring at 6 to 10 minutes. The duration and degree of reversal are related to the plasma concentration of the sedating benzodiazepine as well as the dose of MAZICON given.
In healthy volunteers, MAZICON did not alter intraocular pressure when given alone and reversed the decrease in intraocular pressure seen after administration of midazolam.
PHARMACOKINETICS: After IV administration, plasma concentrations of flumazenil follow a two compartment open pharmacokinetic model with an initial distribution half-life of 7 to 15 minutes and a terminal half-life of 41 to 79 minutes. Peak concentrations of flumazenil are proportional to dose, with an apparent initial volume of distribution of 0.5 L/kg. After redistribution the apparent volume of distribution (V_{ss}) ranges from 0.77 to 1.60 L/kg. Protein binding is approximately 50% and the drug shows no preferential partitioning into red blood cells. Flumazenil is a highly extracted drug. Clearance of flumazenil occurs primarily by hepatic metabolism and is dependent on hepatic blood flow. In pharmacokinetic studies of normal volunteers, total clearance ranges from 0.7 to 1.3 L/hr/kg, with less than 1% of the administered dose eliminated unchanged in the urine. The major metabolites of flumazenil identified in urine are the de-ethylated free acid and its glucuronide conjugate. In preclinical studies there was no evidence of pharmacologic activity exhibited by the de-ethylated free acid. Elimination of radiolabelled drug is essentially complete within 72 hours, with 90% to 95% of the radioactivity appearing in urine and 5% to 10% in the feces.

Pharmacokinetic Parameters Following a 5-minute Infusion of a total of 1.0 mg of MAZICON Mean (Coefficient of variation, Range)

C_{max} (ng/mL)	24 (38%, 11-43)
AUC (ng•hr/mL)	15 (22%, 10-22)
V_{ss} (L/kg)	1 (24%, 0.8-1.6)
Cl (L/hr/kg)	1 (20%, 0.7-1.4)
Half-life (min)	54 (21%, 41-79)

The pharmacokinetics of flumazenil are not significantly affected by gender, age, renal failure (creatinine clearance <10 mL/min), or hemodialysis beginning 1 hour after drug administration. Mean total clearance is decreased to 40% to 60% of normal in patients with moderate liver dysfunction and to 25% of normal in patients with severe liver dysfunction compared with age-matched healthy subjects. This results in a prolongation of the half-life from 0.8 hours in healthy subjects to 1.3 hours in patients with moderate hepatic impairment and 2.4 hours in severely impaired patients. Ingestion of food during an intravenous infusion of the drug results in a 50% increase in clearance, most likely due to the increased hepatic blood flow that accompanies a meal. The pharmacokinetic profile of flumazenil is unaltered in the presence of benzodiazepine agonists and the kinetic profiles of those benzodiazepines are unaltered by flumazenil.

CLINICAL TRIALS: MAZICON has been administered to reverse the effects of benzodiazepines in conscious sedation, general anesthesia, and the management of suspected benzodiazepine overdose.
CONSCIOUS SEDATION: MAZICON was studied in four trials in 970 patients who received an average of 30 mg diazepam or 10 mg midazolam for sedation (with or without a narcotic) in conjunction with both inpatient and outpatient diagnostic or surgical procedures. MAZICON was effective in reversing the sedating and psychomotor effects of the benzodiazepine, however, amnesia was less completely and less consistently reversed. In these studies, MAZICON was administered as an initial dose of 0.4 mg I.V. (two doses of 0.2 mg) with additional 0.2 mg doses as needed to achieve complete awakening, up to a maximum total dose of 1.0 mg. Seventy-eight percent of patients receiving flumazenil responded by becoming completely alert. Of those patients, approximately half responded to doses of 0.4 to 0.6 mg, while the other half responded to doses of 0.8 to 1.0 mg. Adverse effects were infrequent in patients who received 1 mg of MAZICON or less, although injection site pain, agitation and anxiety did occur. Reversal of sedation was not associated with any increase in the frequency of inadequate analgesia or increase in narcotic demand in these studies. While most patients remained alert throughout the 3 hour post-procedure observation period, resedation was observed to occur in 3% to 9% of the patients, and was most common in patients who had received high doses of benzodiazepine. (See PRECAUTIONS.)
GENERAL ANESTHESIA: MAZICON was studied in four trials in 644 patients who received midazolam as an induction and/or maintenance agent in both balanced and inhalational anesthesia. Midazolam was generally administered in doses ranging from 5 to 80 mg, alone and/or in conjunction with muscle relaxants, nitrous oxide, regional or local anesthetics, narcotics and/or inhalational anesthetics. Flumazenil was given as an initial dose of 0.2 mg IV, with additional 0.2 mg doses as needed to reach a complete response, up to a maximum total dose of 1.0 mg. These doses were effective in reversing sedation and restoring psychomotor function, but did not completely restore memory as tested by picture recall. MAZICON was not as effective in the reversal of sedation in patients who had received multiple anesthetic agents in addition to benzodiazepines.
Eighty-one percent of patients sedated with midazolam responded to flumazenil by becoming completely alert or just slightly drowsy. Of those patients, 36% responded to doses of 0.4 to 0.6 mg, while 64% responded to doses of 0.8 to 1.0 mg.
Resedation in patients who responded to MAZICON occurred in 10% to 15% of patients studied and was more common with larger doses of midazolam (>20 mg), long procedures (>60 minutes) and use of neuromuscular blocking agents. (See PRECAUTIONS.)
MANAGEMENT OF SUSPECTED BENZODIAZEPINE OVERDOSE: MAZICON was studied in two trials in 497 patients who were presumed to have taken an overdose of a benzodiazepine, either alone or in combination with a variety of other agents. In these trials, 299 patients were proven to have taken a benzodiazepine as part of the overdose, and 80% of the 148 who received MAZICON responded by an improvement in level of consciousness. Of the patients who responded to flumazenil, 75% responded to a total dose of 1.0 to 3.0 mg. Reversal of sedation was associated with an increased frequency of symptoms of CNS excitation. Of the

patients treated with flumazenil, 1% to 3% were treated for agitation or anxiety. Serious side effects were uncommon, but six seizures were observed in 446 patients treated with flumazenil in these studies. Four of these 6 patients had ingested a large dose of cyclic antidepressants, which increased the risk of seizures. (See WARNINGS.)

INDIVIDUALIZATION OF DOSAGE: GENERAL PRINCIPLES: The serious adverse effects of MAZICON are related to the reversal of benzodiazepine effects. Using more than the minimally effective dose of MAZICON is tolerated by most patients but may complicate the management of patients who are physically dependent on benzodiazepines or patients who are depending on benzodiazepines for therapeutic effect (such as suppression of seizures in cyclic antidepressant overdose).
In high-risk patients, it is important to administer the smallest amount of MAZICON that is effective. The 1-minute wait between individual doses in the dose-titration recommended for general clinical populations may be too short for high risk patients. This is because it takes 6 to 10 minutes for any single dose of flumazenil to reach full effects. Practitioners should slow the rate of administration of MAZICON administered to high risk patients as recommended below.
ANESTHESIA AND CONSCIOUS SEDATION: MAZICON is well tolerated at the recommended doses in individuals who have no tolerance to (or dependence on) benzodiazepines. The recommended dosages and titration rates in anesthesia and conscious sedation (0.2 to 1.0 mg given at 0.2 mg/min) are well tolerated in patients receiving the drug for reversal of a single benzodiazepine exposure in most clinical settings (see Adverse Events). The major risk will be resedation because the duration of effect of a long-acting (or large dose of a short-acting) benzodiazepine may exceed that of MAZICON. Resedation may be treated by giving a repeat dose at no less than 20-minute intervals. For repeat treatment, no more than 1.0 mg (at 0.2 mg/min doses) should be given at any one time and no more than 3.0 mg should be given in any one hour.
OVERDOSE PATIENTS: The risk of confusion, agitation, emotional lability and perceptual distortion with the doses recommended in patients with benzodiazepine overdose (3 to 5 mg administered as 0.5 mg/min) may be greater than that expected with lower doses and slower administration. The recommended doses represent a compromise between a desirable slow awakening and the need for prompt response and a persistent effect in the overdose situation. If circumstances permit, the physician may elect to use the 0.2 mg/minute titration rate to slowly awaken the patient over 5 to 10 minutes, which may help to reduce signs and symptoms on emergence.
MAZICON has no effect in cases where benzodiazepines are not responsible for sedation. Once doses of 3 to 5 mg have been reached without clinical response, additional MAZICON is likely to have no effect.
PATIENTS TOLERANT TO BENZODIAZEPINES: MAZICON may cause benzodiazepine withdrawal symptoms in individuals who have been taking benzodiazepines long enough to have some degree of tolerance. Patients who had been taking benzodiazepines prior to entry into the MAZICON trials who were given flumazenil in doses over 1 mg experienced withdrawal-like events 2 to 5 times more frequently than patients who received less than 1 mg.
In patients who may have tolerance to benzodiazepines, as indicated by clinical history or by the need for larger than usual doses of benzodiazepine, slower titration rates of 0.1 mg/min and lower total doses may help reduce the frequency of emergent confusion and agitation. In such cases special care must be taken to monitor the patients for resedation because of the lower doses of MAZICON used.
PATIENTS PHYSICALLY DEPENDENT ON BENZODIAZEPINES: MAZICON is known to precipitate withdrawal seizures in patients who are physically dependent on benzodiazepines, even if such dependence was established in a relatively few days of high dose sedation in Intensive Care Unit environments. The risk of either seizures or resedation in such cases is high and patients have experienced seizures before regaining consciousness. MAZICON should be used in such settings with extreme caution, since the use of flumazenil in this situation has not been studied and no information as to dose and rate of titration is available. MAZICON should be used in such patients only if the potential benefits of using the drug outweigh the risks of precipitated seizures. Physicians are directed to the scientific literature for the most current information in this area.

INDICATIONS AND USAGE: MAZICON is indicated for the complete or partial reversal of the sedative effects of benzodiazepines in cases where general anesthesia has been induced and/or maintained with benzodiazepines, where sedation has been produced with benzodiazepines for diagnostic and therapeutic procedures, and for the management of benzodiazepine overdose.

CONTRAINDICATIONS: MAZICON is contraindicated:
- In patients with a known hypersensitivity to flumazenil or to benzodiazepines.
- In patients who have been given a benzodiazepine for control of a potentially life-threatening condition (*e.g.* control of intracranial pressure or status epilepticus).
- In patients who are showing signs of serious cyclic antidepressant overdose. (See WARNINGS.)

WARNINGS:

THE USE OF MAZICON HAS BEEN ASSOCIATED WITH THE OCCURRENCE OF SEIZURES.
THESE ARE MOST FREQUENT IN PATIENTS WHO HAVE BEEN ON BENZODIAZEPINES FOR LONG-TERM SEDATION OR IN OVERDOSE CASES WHERE PATIENTS ARE SHOWING SIGNS OF SERIOUS CYCLIC ANTIDEPRESSANT OVERDOSE.
PRACTITIONERS SHOULD INDIVIDUALIZE THE DOSAGE OF MAZICON AND BE PREPARED TO MANAGE SEIZURES.

Risk of Seizures: The reversal of benzodiazepine effects may be associated with the onset of seizures in certain high-risk populations. Possible risk factors for seizures include: concurrent major sedative-hypnotic drug withdrawal, recent therapy with repeated doses of parenteral benzodiazepines, myoclonic jerking or seizure activity prior to flumazenil administration in overdose cases, or concurrent cyclic antidepressant poisoning.
MAZICON is not recommended in cases of serious cyclic antidepressant poisoning, as manifested by motor abnormalities (twitching, rigidity, focal seizure), dysrhythmia (wide QRS, ventricular dysrhythmia, heart block), anticholinergic signs (mydriasis, dry mucosa, hypo-peristalsis), and cardiovascular collapse at presentation. In such cases MAZICON should be withheld and the patient should be allowed to remain sedated (with ventilatory and circulatory support as needed) until the signs of antidepressant toxicity have subsided. Treatment with MAZICON has no known benefit to the seriously ill mixed-overdose patient other than reversing sedation and should not be used in cases where seizures (from any cause) are likely.
Most convulsions associated with flumazenil administration require treatment and have been successfully managed with benzodiazepines, phenytoin or barbiturates. Because of the presence of flumazenil, higher than usual doses of benzodiazepines may be required.

HYPOVENTILATION: Patients who have received MAZICON for the reversal of benzodiazepine effects (after conscious sedation or general anesthesia) should be monitored for resedation, respiratory depression, or other residual benzodiazepine effects for an appropriate period (up to 120 minutes) based on the dose and duration of effect of the benzodiazepine employed.
This is because MAZICON has not been established as an effective treatment for hypoventilation due to benzodiazepine administration. The availability of flumazenil does not diminish the need for prompt detection of hypoventilation and the ability to effectively intervene by establishing an airway and assisting ventilation.
MAZICON may not fully reverse postoperative airway problems or ventilatory insufficiency induced by benzodiazepines. In addition, even if MAZICON is initially effective, such problems may recur because the effects of MAZICON wear off before the effects of many benzodiazepines.
Overdose cases should always be monitored for resedation until the patients are stable and resedation is unlikely.

PRECAUTIONS: RETURN OF SEDATION: MAZICON may be expected to improve the alertness of patients recovering from a procedure involving sedation or anesthesia with benzodiazepines, but should not be substituted for an adequate period of post-procedure monitoring. The availability of MAZICON does not reduce the risks associated with the use of large doses of benzodiazepines for sedation.
Patients should be monitored for resedation, respiratory depression (see WARNINGS), or other persistent or recurrent agonist effects for an adequate period of time after administration of MAZICON.
Resedation is least likely in cases where MAZICON is administered to reverse a low dose of a short-acting benzodiazepine (<10 mg midazolam). It is most likely in cases where a large single or cumulative dose of a benzodiazepine has been given in the course of a long procedure along with neuromuscular blocking agents and multiple anesthetic agents.
Profound resedation was observed in 1% to 3% of patients in the clinical studies. In clinical situations where resedation must be prevented, physicians may wish to repeat the initial dose (up to 1 mg of MAZICON given at 0.2 mg/min) at 30 minutes and possibly again at 60 minutes. This dosage schedule, although not studied in clinical trials, was effective in preventing resedation in a pharmacologic study in normal volunteers.
USE IN THE ICU: MAZICON should be used with caution in the Intensive Care Unit because of the increased risk of unrecognized benzodiazepine dependence in such settings. MAZICON may produce convulsions in patients physically dependent on benzodiazepines. (See INDIVIDUALIZATION OF DOSAGE AND WARNINGS.)
Administration of MAZICON to diagnose benzodiazepine-induced sedation in the Intensive Care Unit is not recommended due to the risk of adverse events as described above. In addition, the prognostic significance of a patient's failure to respond to flumazenil in cases confounded by metabolic disorder, traumatic injury, drugs other than benzodiazepines, or any other reasons not associated with benzodiazepine receptor occupancy is not known.

USE IN OVERDOSE: MAZICON is intended as an adjunct to, not as a substitute for, proper management of airway, assisted breathing, circulatory access and support, internal decontamination by lavage and charcoal, and adequate clinical evaluation.

Necessary measures should be instituted to secure airway, ventilation and intravenous access prior to administering flumazenil. Upon arousal patients may attempt to withdraw endotracheal tubes and/or intravenous lines as the result of confusion and agitation following awakening.

HEAD INJURY: MAZICON should be used with caution in patients with head injury as it may be capable of precipitating convulsions or altering cerebral blood flow in patients receiving benzodiazepines. It should be used only by practitioners prepared to manage such complications should they occur.

USE WITH NEUROMUSCULAR BLOCKING AGENTS: MAZICON should not be used until the effects of neuromuscular blockade have been fully reversed.

USE IN PSYCHIATRIC PATIENTS: MAZICON has been reported to provoke panic attacks in patients with a history of panic disorder.

PAIN ON INJECTION: To minimize the likelihood of pain or inflammation at the injection site, MAZICON should be administered through a freely flowing intravenous infusion into a large vein. Local irritation may occur following extravasation into perivascular tissues.

USE IN RESPIRATORY DISEASE: The primary treatment of patients with serious lung disease who experience serious respiratory depression due to benzodiazepines should be appropriate ventilatory support (See PRECAUTIONS) rather than the administration of MAZICON. Flumazenil is capable of partially reversing benzodiazepine-induced alterations in ventilatory drive in healthy volunteers, but has not been shown to be clinically effective.

USE IN CARDIOVASCULAR DISEASE: MAZICON did not increase the work of the heart when used to reverse benzodiazepines in cardiac patients when given at a rate of 0.1 mg/min in total doses of less than 0.5 mg in studies reported in the clinical literature. Flumazenil alone had no significant effects on cardiovascular parameters when administered to patients with stable ischemic heart disease.

USE IN LIVER DISEASE: The clearance of MAZICON is reduced to 40% to 60% of normal in patients with mild to moderate hepatic disease and to 25% of normal in patients with severe hepatic dysfunction. (See PHARMACOKINETICS.) While the dose of flumazenil used for initial reversal of benzodiazepine effects is not affected, repeat doses of the drug in liver disease should be reduced in size or frequency.

USE IN DRUG AND ALCOHOL DEPENDENT PATIENTS: MAZICON should be used with caution in patients with alcoholism and other drug dependencies due to the increased frequency of benzodiazepine tolerance and dependence observed in these patient populations.

MAZICON is not recommended either as a treatment for benzodiazepine dependence or for the management of protracted benzodiazepine abstinence syndromes, as such use has not been studied.

The administration of flumazenil can precipitate benzodiazepine withdrawal in animals and man. This has been seen in healthy volunteers treated with therapeutic doses of oral lorazepam for up to 2 weeks who exhibited effects such as hot flushes, agitation and tremor when treated with cumulative doses of up to 3 mg doses of flumazenil.

Similar adverse experiences suggestive of flumazenil precipitation of benzodiazepine withdrawal have occurred in some patients in clinical trials. Such patients had a short-lived syndrome characterized by dizziness, mild confusion, emotional lability, agitation (with signs and symptoms of anxiety), and mild sensory distortions. This response was dose-related, most common at doses above 1 mg, rarely required treatment other than reassurance and was usually short lived. When required (5 to 10 cases), these patients were successfully treated with usual doses of a barbiturate, a benzodiazepine, or other sedative drug.

Practitioners should assume that flumazenil administration may trigger dose-dependent withdrawal syndromes in patients with established physical dependence on benzodiazepines and may complicate the management of withdrawal syndromes for alcohol, barbiturates and cross-tolerant sedatives.

DRUG INTERACTIONS: Interaction with central nervous system depressants other than benzodiazepines has not been specifically studied; however, no deleterious interactions were seen when MAZICON was administered after narcotics, inhalational anesthetics, muscle relaxants and muscle relaxant antagonists administered in conjunction with sedation or anesthesia.

Particular caution is necessary when using MAZICON in cases of mixed drug overdosage since the toxic effects (such as convulsions and cardiac dysrhythmias) of other drugs taken in overdose (especially cyclic antidepressants) may emerge with the reversal of the benzodiazepine effect by flumazenil. (See WARNINGS.)

The pharmacokinetics of benzodiazepines are unaltered in the presence of flumazenil.

USE IN AMBULATORY PATIENTS: The effects of MAZICON may wear off before a long-acting benzodiazepine is completely cleared from the body. In general, if a patient shows no signs of sedation within 2 hours after a 1.0 mg dose of flumazenil, serious resedation at a later time is unlikely. An adequate period of observation must be provided for any patient in whom either long-acting benzodiazepines (such as diazepam) or large doses of short-acting benzodiazepines (such as >10 mg of midazolam) have been used. (See INDIVIDUALIZATION OF DOSAGE.)

Because of the increased risk of adverse reactions in patients who have been taking benzodiazepines on a regular basis, it is particularly important that physicians query carefully about benzodiazepine, alcohol and sedative use as part of the history prior to any procedure in which the use of MAZICON is planned. (See DRUG AND ALCOHOL DEPENDENT PATIENTS.)

INFORMATION FOR PATIENTS: MAZICON does not consistently reverse amnesia. Patients cannot be expected to remember information told to them in the post-procedure period and instructions given to patients should be reinforced in writing or given to a responsible family member. Physicians are advised to discuss with their patients, both before surgery and at discharge, that although the patient may feel alert at the time of discharge, the effects of the benzodiazepine may recur. As a result, the patient should be instructed, preferably in writing, that their memory and judgment may be impaired and specifically advised:

1. Not to engage in any activities requiring complete alertness, and not to operate hazardous machinery or a motor vehicle until at least 18 to 24 hours after discharge, and it is certain no residual sedative effects of the benzodiazepine remain.
2. Not to take any alcohol or non-prescription drugs for 18 to 24 hours after flumazenil administration or if the effects of the benzodiazepine persist.

LABORATORY TESTS: No specific laboratory tests are recommended to follow the patient's response or to identify possible adverse reactions.

DRUG/LABORATORY TEST INTERACTIONS: The possible interaction of flumazenil with commonly used laboratory tests has not been evaluated.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Carcinogenesis: No studies in animals to evaluate the carcinogenic potential of flumazenil have been conducted.

Mutagenesis: No evidence for mutagenicity was noted in the Ames test using five different tester strains. Assays for mutagenic potential in *S. cerevisiae* D7 and in Chinese hamster cells were considered to be negative as were blastogenesis assays *in vitro* in peripheral human lymphocytes and *in vivo* in a mouse micronucleus assay. Flumazenil caused a slight increase in unscheduled DNA synthesis in rat hepatocyte culture at concentrations which were also cytotoxic; no increase in DNA repair was observed in male mouse germ cells in an *in vivo* DNA repair assay.

Impairment of fertility: A reproduction study in male and female rats did not show any impairment of fertility at oral dosages of 125 mg/kg/day. From the available data on the area under the curve (AUC) in animals and man the dose represented 120 x the human exposure from a maximum recommended intravenous dose of 5 mg.

PREGNANCY: CATEGORY C. There are no adequate and well-controlled studies of the use of flumazenil in pregnant women. Flumazenil should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Teratogenic Effects: Flumazenil has been studied for teratogenicity in rats and rabbits following oral treatments of up to 150 mg/kg/day. The treatments during the major organogenesis were on days 6 to 15 of gestation in the rat and days 6 to 18 of gestation in the rabbit. No teratogenic effects were observed in rats or rabbits at 150 mg/kg; the dose, based on the available data on the area under the plasma concentration-time curve (AUC) represented 120 x to 600 x the human exposure from a maximum recommended intravenous dose of 5 mg in humans. In rabbits, embryocidal effects (as evidenced by increased pre-implantation and post-implantation losses) were observed at 50 mg/kg or 200 x the human exposure from a maximum recommended intravenous dose of 5 mg. The no-effect dose of 15 mg/kg in rabbits represents 60 x the human exposure.

Nonteratogenic Effects: An animal reproduction study was conducted in rats at oral dosages of 5, 25 and 125 mg/kg/day of flumazenil. Pup survival was decreased during the lactating period, pup liver weight at weaning was increased for the high-dose group (125 mg/kg/day) and incisor eruption and ear opening in the offspring were delayed; the delay in ear opening was associated with a delay in the appearance of the auditory startle response. No treatment-related adverse effects were noted for the other dose groups. Based on the available data from AUC, the effect level (125 mg/kg), represents 120 x the human exposure from 5 mg, the maximum recommended intravenous dose in humans. The no-effect level represents 24 x the human exposure from an intravenous dose of 5 mg.

LABOR AND DELIVERY: The use of MAZICON to reverse the effects of benzodiazepines used during labor and delivery is not recommended because the effects of the drug in the newborn are unknown.

NURSING MOTHERS: Caution should be exercised when deciding to administer MAZICON to a nursing woman because it is not known whether flumazenil is excreted in human milk.

PEDIATRIC USE: MAZICON is not recommended for use in children (either for the reversal of sedation, the management of overdose or the resuscitation of the newborn), as no clinical studies have been performed to determine the risks, benefits and dosages to be used.

GERIATRIC USE: The pharmacokinetics of flumazenil have been studied in the elderly and are not significantly different from younger patients. Several studies of MAZICON in patients over the age of 65 and one study in patients over the age of 80 suggest that while the doses of benzodiazepine used to induce sedation should be reduced, ordinary doses of MAZICON may be used for reversal.

ADVERSE REACTIONS: SERIOUS ADVERSE REACTIONS: Deaths have occurred in patients who received MAZICON in a variety of clinical settings. The majority of deaths occurred in patients with serious underlying disease or in patients who had ingested large amounts of non-benzodiazepine drugs, (usually cyclic antidepressants) as part of an overdose.

Serious adverse events have occurred in all clinical settings, and convulsions are the most common serious adverse event reported. MAZICON administration has been associated with the onset of convulsions in patients who are relying on benzodiazepine effects to control seizures, are physically dependent on benzodiazepines, or who have ingested large doses of other drugs. (See WARNINGS.)

Two of the 446 patients who received MAZICON in controlled clinical trials for the management of a benzodiazepine overdosage had cardiac dysrhythmias (1 ventricular tachycardia, 1 junctional tachycardia).

ADVERSE EVENTS IN CLINICAL STUDIES: The following adverse reactions were considered to be related to MAZICON administration (both alone and for the reversal of benzodiazepine effects) and were reported in studies involving 1875 individuals who received flumazenil in controlled trials. Adverse events most frequently associated with flumazenil alone were limited to dizziness, injection site pain, increased sweating, headache and abnormal or blurred vision (3% to 9%).

BODY AS A WHOLE: Fatigue (asthenia, malaise), Headache, Injection Site Pain*, Injection Site Reaction (thrombophlebitis, skin abnormality, rash)

CARDIOVASCULAR SYSTEM: Cutaneous vasodilation (sweating, flushing, hot flushes)

DIGESTIVE SYSTEM: Nausea and Vomiting (11%)

NERVOUS SYSTEM: Agitation (anxiety, nervousness, dry mouth, tremor, palpitations, insomnia, dyspnea, hyperventilation)*, Dizziness (vertigo, ataxia) (10%), Emotional lability (crying abnormal, depersonalization, euphoria, increased tears, depression, dysphoria, paranoia).

SPECIAL SENSES: Abnormal Vision (visual field defect, diplopia), Paresthesia (sensation abnormal, hypoesthesia)

All adverse reactions occurred in 1% to 3% of cases unless otherwise marked.

*indicates reaction in 3% to 9% of cases.

Observed percentage reported if greater than 9%.

The following adverse events were observed infrequently (less than 1%) in the clinical studies, but were judged as probably related to MAZICON administration and/or reversal of benzodiazepine effects:

NERVOUS SYSTEM: Confusion (difficulty concentrating, delirium), Convulsions (see WARNINGS), Somnolence (stupor).

SPECIAL SENSES: Abnormal Hearing (transient hearing impairment, hyperacusis, tinnitus).

The following adverse events occurred with frequencies less than 1% in the clinical trials. Their relationship to MAZICON administration is unknown, but they are included as alerting information for the physician.

BODY AS A WHOLE: Rigors, shivering.

CARDIOVASCULAR: Arrhythmia (atrial, nodal, ventricular extrasystoles), bradycardia, tachycardia, hypertension, chest pain.

DIGESTIVE SYSTEM: Hiccup.

NERVOUS SYSTEM: Speech disorder (dysphonia, thick tongue).

Not included in this list is operative site pain that occurred with the same frequency in patients receiving placebo as in patients receiving flumazenil for reversal of sedation following a surgical procedure.

DRUG ABUSE AND DEPENDENCE: MAZICON acts as a benzodiazepine antagonist, blocks the effects of benzodiazepines in animals and man, antagonizes benzodiazepine reinforcement in animal models, produces dysphoria in normal subjects, and has had no reported abuse in foreign marketing.

Although MAZICON has a benzodiazepine-like structure it does not act as a benzodiazepine agonist in man and is not a controlled substance.

OVERDOSAGE: Large intravenous doses of MAZICON, when administered to healthy normal volunteers in the absence of a benzodiazepine agonist, produced no serious adverse reactions, severe signs or symptoms, or clinically significant laboratory test abnormalities. In clinical studies, most adverse reactions to flumazenil were an extension of the pharmacologic effects of the drug in reversing benzodiazepine effects.

Reversal with an excessively high dose of MAZICON may produce anxiety, agitation, increased muscle tone, hyperesthesia and possibly convulsions. Convulsions have been treated with barbiturates, benzodiazepines and phenytoin, generally with prompt resolution of the seizures. (See WARNINGS.)

DOSE AND ADMINISTRATION: MAZICON is recommended for intravenous use only. It is compatible with 5% dextrose in water, lactated Ringer's and normal saline solutions. If MAZICON is drawn into a syringe or mixed with any of these solutions, it should be discarded after 24 hours. For optimum sterility, MAZICON should remain in the vial until just before use. As with all parenteral drug products, MAZICON should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

To minimize the likelihood of pain at the injection site, MAZICON should be administered through a freely running intravenous infusion into a large vein.

REVERSAL OF CONSCIOUS SEDATION OR IN GENERAL ANESTHESIA: For the reversal of the sedative effects of benzodiazepines administered for conscious sedation or general anesthesia, the recommended initial dose of MAZICON is 0.2 mg (2 mL) administered intravenously over 15 seconds. If the desired level of consciousness is not obtained after waiting an additional 45 seconds, a further dose of 0.2 mg (2 mL) can be injected and repeated at 60-second intervals where necessary (up to a maximum of 4 additional times) to a maximum total dose of 1 mg (10 mL). The dose should be individualized based on the patient's response, with most patients responding to doses of 0.6 to 1 mg. (See INDIVIDUALIZATION OF DOSAGE.)

In the event of resedation, repeated doses may be administered at 20 minute intervals as needed. For repeat treatment, no more than 1 mg (given as 0.2 mg/min) should be administered at any one time, and no more than 3 mg should be given in any one hour.

It is recommended that MAZICON be administered as the series of small injections described (not as a single bolus injection) to allow the practitioner to control the reversal of sedation to the approximate endpoint desired and to minimize the possibility of adverse effects. (See INDIVIDUALIZATION OF DOSAGE.)

MANAGEMENT OF SUSPECTED BENZODIAZEPINE OVERDOSE: For initial management of a known or suspected benzodiazepine overdose, the recommended initial dose of MAZICON is 0.2 mg (2 mL) administered intravenously over 30 seconds. If the desired level of consciousness is not obtained after waiting 30 seconds, a further dose of 0.3 mg (3 mL) can be administered over another 30 seconds. Further doses of 0.5 mg (5 mL) can be administered over 30 seconds at 1-minute intervals up to a cumulative dose of 3 mg.

Do not rush the administration of MAZICON. Patients should have a secure airway and intravenous access before administration of the drug and be awakened gradually. (See PRECAUTIONS.)

Most patients with benzodiazepine overdose will respond to a cumulative dose of 1-3 mg of MAZICON, and doses beyond 3 mg do not reliably produce additional effects. On rare occasions, patients with a partial response at 3 mg may require additional titration up to a total dose of 5 mg (administered slowly in the same manner).

If a patient has not responded 5 minutes after receiving a cumulative dose of 5 mg MAZICON, the major cause of sedation is likely not to be due to benzodiazepines, and additional MAZICON is likely to have no effect.

In the event of resedation, repeated doses may be given at 20-minute intervals if needed. For repeat treatment, no more than 1 mg (given as 0.5 mg/min) should be given at any one time and no more than 3 mg should be given in any one hour.

SAFETY AND HANDLING: MAZICON is supplied in sealed dosage forms and poses no known risk to the health care provider. Routine care should be taken to avoid aerosol generation when preparing syringes for injection, and spilled medication should be rinsed from the skin with cool water.

HOW SUPPLIED: 5 mL multiple-use vials containing 0.1 mg/mL flumazenil:
Boxes of 10 (NDC 0004-6904-14).
10 mL multiple-use vials containing 0.1 mg/mL flumazenil:
Boxes of 10 (NDC 0004-6905-14).
Store at 59° to 86° F (15° to 30° C).

REVISED: APRIL 1992

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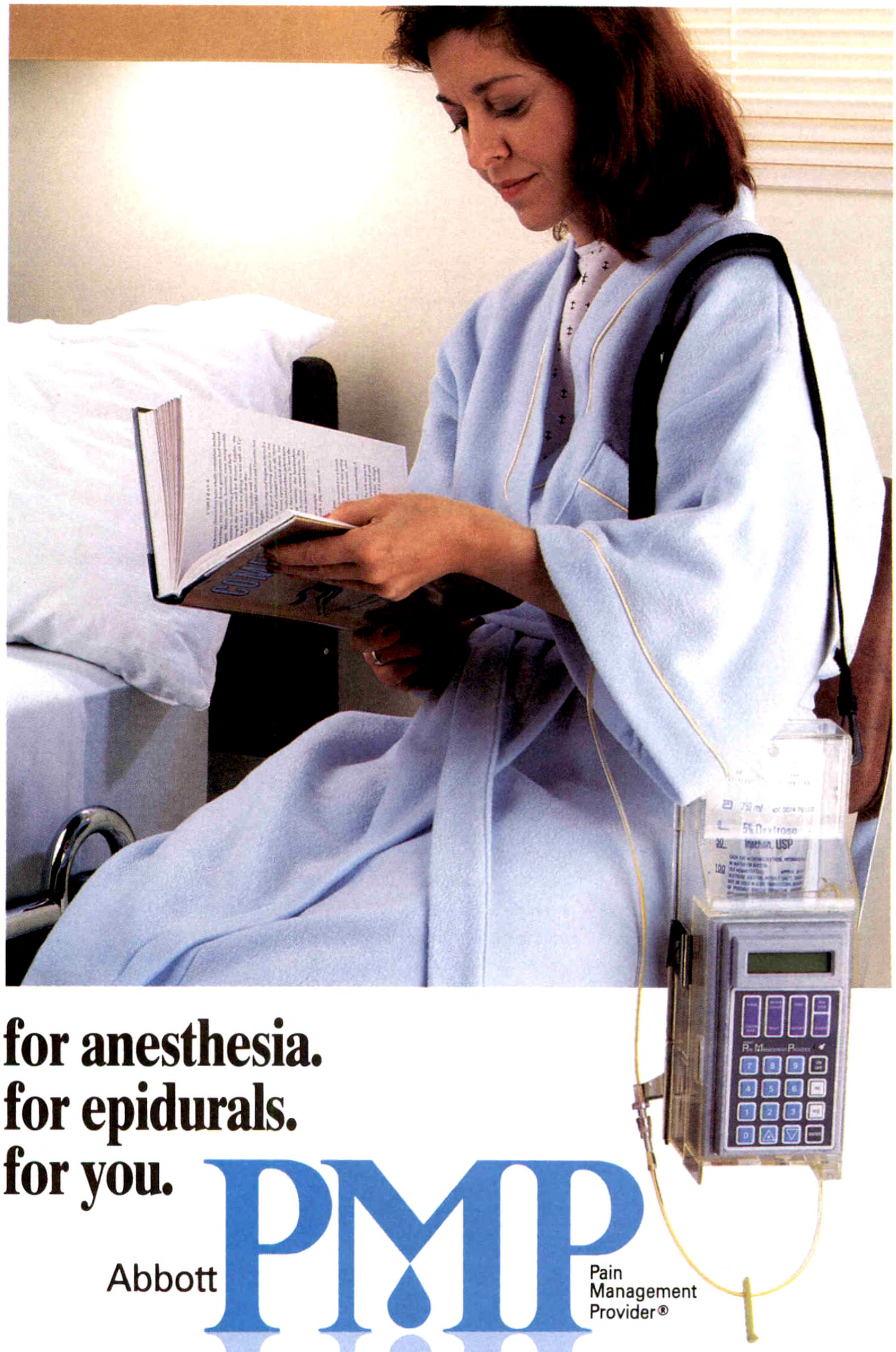

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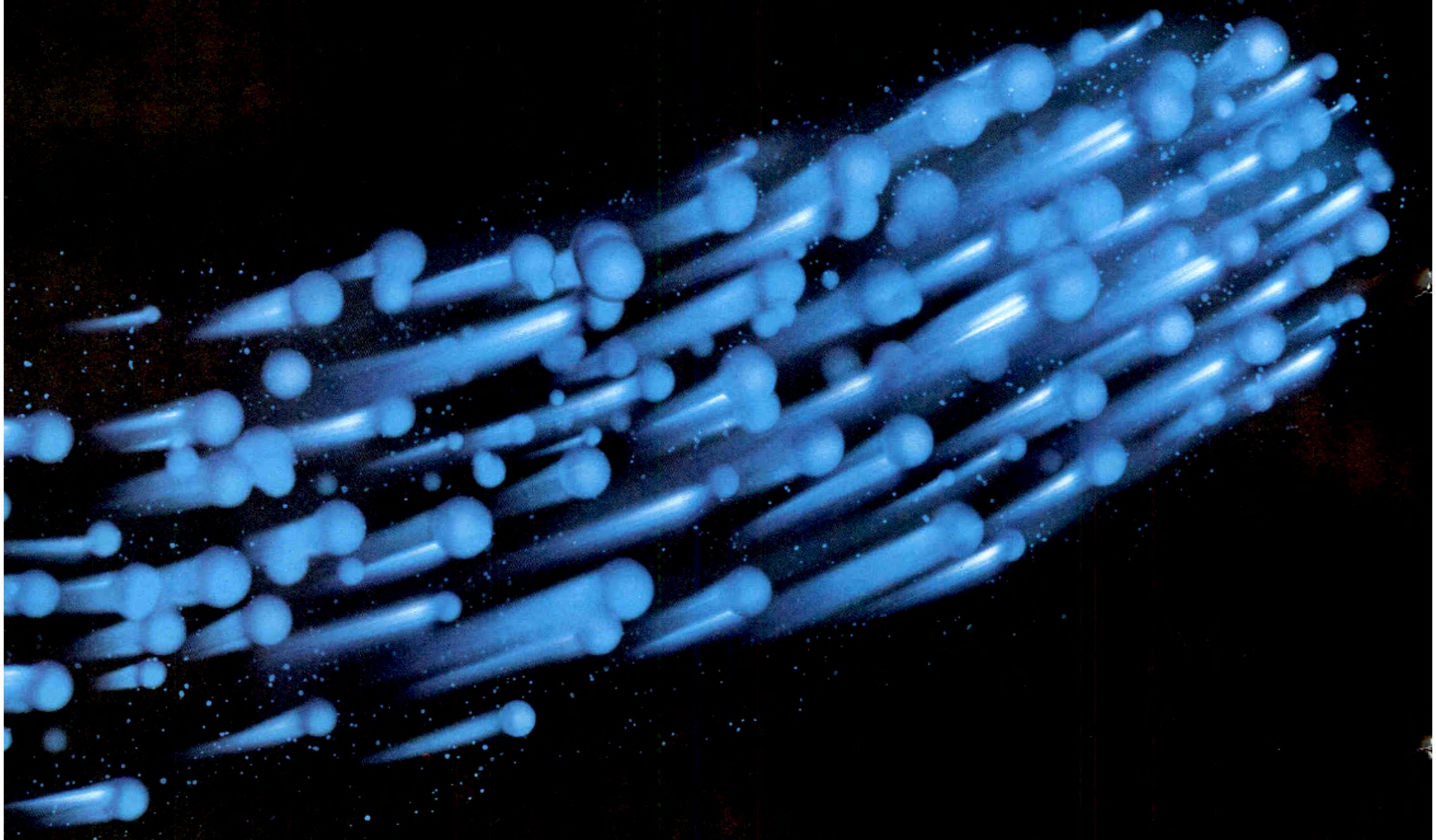

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Nitrous Oxide Impairs Functional Recovery of Stunned Myocardium in Barbiturate-Anesthetized, Acutely Instrumented Dogs

Daniel Siker, MD, Paul S. Pagel, MD, Lorie R. Pelc, PhD, John P. Kampine, MD, PhD, William T. Schmeling, MD, PhD, and David C. Warltier, MD, PhD

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The purpose of this investigation was to characterize the effects of nitrous oxide or nitrogen (70%) on systemic and regional hemodynamics and myocardial tissue perfusion after a brief coronary artery occlusion (15 min) and reperfusion (3 h). Two groups of experiments (14 experiments total) were completed with 24 open-chest, barbiturate-anesthetized dogs. Coronary collateral blood flow was diverted from the ischemic zone during coronary artery occlusion to eliminate a source of variability in degree of ischemia produced by differences in degrees of collateral blood flow among animals. Seven of 16 dogs treated with nitrous oxide and 7 of 8 dogs treated with nitrogen survived coronary occlusion and reperfusion ($P < 0.05$). Coronary artery occlusion produced paradoxical systolic bulging in the ischemic zone in both groups of experiments. After reperfusion, segment shortening gradually returned toward control levels but remained depressed from the preocclusion state after 3 h in the nitrogen-treated control group. Similar results were observed after reperfusion in the nitrous oxide group; however, segment function in the ischemic region was significantly ($P < 0.05$) depressed throughout the 3-h reperfusion period compared with the control group. Transmural coronary collateral blood flow during occlusion was not significantly different ($P > 0.05$) between groups, indicating that differences in recovery of contractile function observed between groups could not be attributed to differences in myocardial oxygen supply. In addition, the similarity in systemic hemodynamics between the nitrous oxide and control groups indirectly suggests that differences in recovery of function could not be attributed to differences in myocardial oxygen demand. The results indicate that 70% nitrous oxide produces greater mortality after coronary artery occlusion and reperfusion and reduces functional recovery of postischemic, reperfused myocardium compared with 70% nitrogen in open-chest, acutely instrumented dogs.

(Anesth Analg 1992;75:539–48)

Reperfusion after brief periods of coronary artery occlusion is associated with delayed recovery of contractile function despite return of blood flow to normal levels (1). This reversible postischemic myocardial dysfunction, termed "stunned" myocardium (2), may be prolonged but occurs without tissue necrosis (3,4). This phenomenon appears to play an important role in the natural history of ischemic heart disease because spontaneous reperfusion of ischemic myocardium after thrombosis or coronary vasospasm is known to occur frequently in patients with coronary artery disease. In addition, patients with acute myocardial ischemia often undergo coronary artery reperfusion through interventions, such as thrombolytic therapy, angioplasty, and emergency bypass surgery, in attempts to salvage myocardium at risk.

The pathogenesis of stunned myocardium remains unclear despite extensive study (3). Although tissue reperfusion is necessary to preserve myocardial integrity, several ischemia-induced cellular abnormalities have been implicated in the subsequent development of reperfusion injury (1,3–7). Intracellular calcium overload (8), depletion of high-energy phosphates (9–11), production of oxygen-derived free radicals (12,13), and uncoupling of myocyte excitation and contraction (14) have all been suggested as contributing etiologies for the contractile dysfunction observed in stunned myocardium. Pharmacologic

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therapy has focused on modulation of these diverse pathophysiologic abnormalities and a variety of treatment modalities, including calcium channel blockers (15–18), vasodilators (15,19), β-adrenergic antagonists (20), specific bradycardic agents (21), and superoxide dismutase and catalase (22), have all been shown to enhance recovery.

The effects of anesthetics on contractile function recovery in postischemic, reperfused myocardium have been examined only recently. Volatile anesthetics have been shown to improve functional recovery of stunned myocardium when these agents are administered in vivo (23) and in vitro (24) before and during, but not after (25), brief periods of myocardial ischemia. The effects of nitrous oxide on stunned myocardium have not been previously described. Use of this anesthetic gas in patients with ischemic heart disease remains controversial. Studies in experimental models of coronary artery constriction have suggested that nitrous oxide may contribute to development of myocardial ischemia (26–31). Most clinical investigations have been unable to confirm these findings in patients with coronary artery disease (32–38). Accordingly, systemic and coronary hemodynamics, regional contractile function, and intramyocardial blood flow, as evaluated by the radioactive microsphere technique, were recorded during brief coronary artery occlusion (15 min) and 3 h of reperfusion in control (70% nitrogen) and nitrous oxide (70%) groups. Because dogs have varying degrees of coronary collateral circulation, retrograde coronary flow was diverted during occlusion to eliminate the variability of endogenous collateral blood flow among animals. The present investigation was performed to characterize actions of nitrous oxide on recovery of function of stunned myocardium in open-chest, barbiturate-anesthetized dogs.

Methods

Experimental Preparation

All experimental procedures and protocols used in this investigation were reviewed and approved by the Animal Care Committee of the Medical College of Wisconsin. Furthermore, all conformed to the *Guiding Principles in the Care and Use of Animals* of the American Physiologic Society and were in accordance with the *Guide for the Care and Use of Laboratory Animals* (DHEW [DHHS] publication No. [NIH] 85-23, revised 1985).

Twenty-four adult male and female mongrel dogs, weighing 25–30 kg, were fasted overnight and anesthetized with sodium pentobarbital (25 mg/kg) and sodium barbital (200 mg/kg). After tracheal intubation, ventilation was controlled (Ohio Medical Products, Airco Inc., Madison, Wis.) with an oxygen (30%)–nitrogen (70%) mixture (1.0 L/min). Respiratory rate and tidal volume were adjusted to maintain arterial blood gases within normal physiologic limits (pH 7.35–7.45; P_{CO_2} 30–35 mm Hg; P_{O_2} 85–100 mm Hg). Temperature was monitored and maintained at 37° ± 1°C (mean ± SE) by a humidified circuit, warming light, and heating pad connected to a servomechanical controller.

Dual-pressure transducer-tipped catheters (SPR-277, Millar, Houston, Tex.) were placed into the left ventricle and ascending aorta through the left carotid artery for measurement of continuous left ventricular and arterial pressures, respectively. Peak positive dP/dt, an index of global left ventricular contractility, was obtained by electronic differentiation of the left ventricular pressure pulse. A triangular wave signal of known slope was used to calibrate the differentiator. The right femoral vein and left femoral artery were catheterized for fluid administration and for withdrawal of reference arterial blood samples, respectively. A thoracotomy was performed at the left fifth intercostal space. The lung was gently retracted, and the heart was suspended in a pericardial cradle. A catheter was placed in the left atrium through the atrial appendage for injection of radioactive microspheres. The right carotid artery was isolated and cannulated. A 1.0–1.5-cm segment of the left anterior descending coronary artery (LAD) was isolated distal to the first diagonal branch and cannulated with a large-bore, metal-tipped catheter. Heparin (300 U/kg) was administered intravenously. Perfusion to the distal LAD was reestablished within 2 min after cannulation via a silastic shunt from the right carotid artery. A cannulating electromagnetic flow probe (Statham SP7515, Gould Instruments, Cleveland, Ohio) for measurement of coronary blood flow was placed proximal to a side arm in the shunt with a three-way stopcock. The stopcock was suspended at the level of the heart and used for passive diversion of coronary collateral blood flow during coronary artery occlusion. A steel clamp was positioned around the silastic shunt immediately distal to the flow probe for production of coronary artery occlusion. The site of LAD cannulation was chosen so that approximately equal regions of the left ventricle were subjected to ischemia in all animals. The mass of the left ventricle subjected to occlusion and reperfusion was 27.7% ± 1.0% (mean ± SE) of the total left ventricular mass in all dogs.

Myocardial contractile function (percent segment shortening [%SS]) was measured in the ischemic (LAD) and normal (left circumflex coronary artery [LCCA]) regions with ultrasonic segment-length transducers (5 MHz) implanted (10–15 mm apart and 7–9 mm deep) into the subendocardium of each region parallel to fiber orientation. Segment-length signals were monitored and driven by an ultrasonic amplifier (Hartley, Houston, Tex.). End-systolic segment length (ESL) was determined at maximal negative dP/dt, and end-diastolic segment length (EDL) was determined at the onset of left ventricular isovolumetric contraction. The lengths were normalized according to the method described by Theroux et al. (39). Percent segment shortening was calculated using the following equation: $\%SS = (EDL - ESL) \times 100/EDL$. All hemodynamic data were continuously recorded on a polygraph (model 7, Grass Instrument Co., Quincy, Mass.).

At the end of each experiment, the heart was electrically fibrillated, immediately removed, and fixed in 10% formaldehyde for 24–48 h. India ink (5 mL) was injected distally through the LAD cannula to darken the area of myocardium subjected to coronary occlusion and reperfusion. The left ventricle and septum was separated from the remainder of the heart, divided into stained and unstained regions, and weighed to determine the mass of the left ventricle subjected to ischemic insult.

Regional Tissue Perfusion

Carbonized plastic microspheres (15 ± 2 μm in diameter) (New England Nuclear, Boston, Mass.) labeled with ^{141}Ce, ^{103}Ru, ^{51}Cr, or ^{95}Nb were used to measure regional tissue perfusion (40). Immediately before injection, the sphere suspension was ultrasonicated (E/MC Corporation, model 450) for 15 min and agitated in a vortex mixer (Cole-Parmer, model 4722) for 5 min. The microsphere injection consisted of approximately 2–3 $\times 10^6$ spheres injected into the left atrial chamber as a bolus dose over 10 s and flushed in with 10 mL of warm (37°C) sterile saline solution. A few seconds before each microsphere injection, a timed collection of reference arterial blood from the femoral arterial catheter was initiated and maintained at a constant rate of 7 mL/min for 3 min (precalibrated Harvard infusion/withdrawal pump, model 1941).

At the conclusion of each experiment, transmural myocardial tissue samples were selected for mapping of regional myocardial blood flow. The samples were subdivided into subepicardial, midmyocardial, and subendocardial layers of approximately equal thickness. Samples were weighed, placed in scintillation vials, and the activity of each isotope was determined. The activity of each isotope in the reference blood samples was also determined. The radioactivity in the tissue and reference blood samples was analyzed with a gamma counter (Minaxi 5000, Packard, Downers Grove, Ill.). Myocardial blood flow (Q_m) ($mL \cdot min^{-1} \cdot g^{-1}$) was calculated from the following equation: $Q_m = Q_r \cdot C_m / C_r$, where Q_r is the rate of withdrawal of the reference blood flow sample (mL/min), C_r is the activity (counts per minute [cpm]) of the reference blood flow sample, and C_m is the activity (cpm/g) of the tissue sample.

Experimental Protocol

Dogs were assigned to receive either nitrous oxide (70%) or nitrogen (70%) in combination with oxygen (30%) before and during LAD occlusion in a random fashion in separate experimental groups. After surgery was completed, the preparation was allowed to stabilize for 30 min during ventilation with room air enriched with oxygen (30%). Control hemodynamics and regional contractile function were then recorded, and a radioactive microsphere injection was completed. Hemodynamics and regional myocardial blood flow were again measured after a 30-min period of equilibration during administration of nitrous oxide (70%) or nitrogen (70%) in oxygen (30%). End-tidal gases were continuously measured by mass spectrometry (Advantage 2000, Marquette Electronics, St. Louis, Mo.). The LAD flow was then interrupted for 15 min by the mechanical occluder in both groups. During LAD occlusion, retrograde LAD coronary flow from the cannulas was allowed to drain by gravity to reduce collateral perfusion within the ischemic zone. After 12 min of LAD occlusion, hemodynamics and segment function were measured, and another set of radioactive microspheres was administered. The occlusion was removed after 15 min, and reperfusion was allowed to occur. All dogs (in both control [nitrogen] and nitrous oxide groups) received lidocaine (1 mg/kg IV) and procainamide (5 mg/kg IV) immediately before reperfusion. Nitrous oxide (70%) or nitrogen (70%) was continued throughout the occlusion and 15 min into the reperfusion period in separate groups. Nitrous oxide was then discontinued, and room air enriched with oxygen (30%) was reinstituted. Hemodynamics and regional myocardial function were recorded at 5, 15, 30, 60, 120, and 180 min during the reperfusion period. A final set of radioactive microspheres was administered at the completion of the 3-h reperfusion period. Thus, systemic hemodynamics, regional myocardial function, and myocardial tissue perfusion before and during acute coronary artery occlusion and during 3 h of reperfusion were studied in control (70% nitrogen) and nitrous oxide (70%)-exposed groups. Twenty-four dogs were used to provide seven experiments in each group.

Statistical Analysis

Statistical analysis of data within and between groups before and during coronary artery occlusion and reperfusion was performed using analysis of variance

Table 1. Hemodynamics During Coronary Artery Occlusion and Reperfusion in Control Experiments in Dogs

	Preocclusion control	Coronary occlusion	Reperfusion (min)					
			5	15	30	60	120	180
HR (beats/min)	121 ± 6	107 ± 4[a]	110 ± 5[a]	111 ± 4[a]	114 ± 5	114 ± 5	123 ± 6	121 ± 5
MAP (mm Hg)	105 ± 10	82 ± 6[a]	84 ± 6[a]	87 ± 6	89 ± 7	92 ± 11	99 ± 10	102 ± 8
LVSP (mm Hg)	125 ± 10	99 ± 6[a]	105 ± 5[a]	107 ± 5[a]	107 ± 7[a]	116 ± 9	124 ± 9	122 ± 9
LVEDP (mm Hg)	4 ± 1	7 ± 1[a]	7 ± 2[a]	7 ± 2[a]	7 ± 2	6 ± 2	6 ± 2	7 ± 2
RPP ($\text{beats}\cdot\text{min}^{-1}\cdot$ mm Hg × 10^3)	14.8 ± 2.0	10.5 ± 0.9[a]	11.2 ± 1.0[a]	11.6 ± 0.9[a]	12.3 ± 1.2[a]	12.6 ± 1.8	14.2 ± 1.8	14.1 ± 12.7
dP/dt (mm Hg/s)	2040 ± 70	1690 ± 110[a]	1660 ± 130[a]	1750 ± 100[a]	1800 ± 120[a]	1860 ± 120	1840 ± 140	1820 ± 120
LAD MCBF (mL/min)	35 ± 5	0 ± 0[a]	57 ± 7[a]	36 ± 6	29 ± 3	27 ± 3	29 ± 4	29 ± 5
LAD SS (%)	19.5 ± 3.3	−3.3 ± 1.5[a]	9.4 ± 2.6[a]	8.1 ± 2.9[a]	8.9 ± 2.9[a]	10.1 ± 2.7[a]	9.8 ± 1.9[a]	7.9 ± 1.9[a]
LCCA SS (%)	10.4 ± 2.7	14.5 ± 3.2	12.0 ± 3.3	10.5 ± 3.3	9.5 ± 2.7	8.9 ± 2.4	8.4 ± 1.9	9.3 ± 2.3

HR, heart rate; MAP, mean arterial pressure; LVSP, left ventricular systolic pressure; LVEDP, left ventricular end-diastolic pressure; RPP, rate-pressure product; LAD, left anterior descending coronary artery; MCBF, mean coronary blood flow; SS, segment shortening; LCCA, left circumflex coronary artery.

Data are mean ± SE ($n = 7$).

[a] Significantly ($P < 0.05$) different from preocclusion control values.

(ANOVA) with repeated measures, followed by application of Bonferroni's modification of the t-test. Changes from control within and between groups were considered statistically significant when the probability (P) value was <0.05. Mortality data between groups were compared with the χ^2 analysis. All data are expressed as mean ± SE.

Results

Twenty-four dogs were used to provide 14 complete stun and reperfusion experiments. Seven of 8 dogs in the control group but only 7 of 16 nitrous oxide-treated dogs survived reperfusion ($P < 0.05$). All deaths were caused by ventricular fibrillation occurring during reperfusion despite prophylactic administration of lidocaine or procainamide. Systemic and coronary hemodynamics during coronary artery occlusion and reperfusion in control experiments are summarized in Table 1. Occlusion of the LAD was accompanied by significant ($P < 0.05$) decreases in heart rate, mean arterial pressure, left ventricular systolic pressure, rate-pressure product, and left ventricular peak positive dP/dt. Significantly ($P < 0.05$) increased left ventricular end-diastolic pressure was observed during acute coronary artery occlusion. These hemodynamic variables recovered to preocclusion levels 30–60 min after the start of reperfusion. Mean LAD blood flow was reduced to zero during occlusion. After a brief reactive hyperemia during the first 5 min of reperfusion, mean coronary blood flow was not statistically different from preocclusion control during the remaining reperfusion period. Occlusion of the LAD resulted in a significant ($P < 0.05$) decrease in percent segment shortening (from 19.5% ± 3.3% during the preocclusion control to −3.3% ± 1.5% during coronary occlusion), indicating regional contractile dysfunction. The paradoxical passive lengthening observed during the period of coronary occlusion in the LAD region was reversed by reperfusion, but segment shortening remained depressed from preocclusion levels throughout the 3-h reperfusion period (Figure 1). No significant changes in segment shortening occurred during occlusion or reperfusion in the normal (LCCA) region (Figure 2).

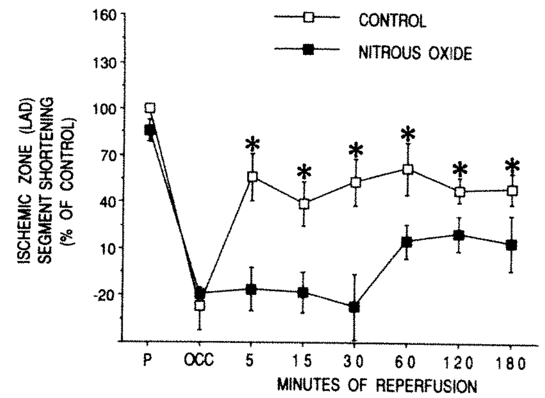

Figure 1. Ischemic zone segment shortening data (mean ± SE) before coronary artery occlusion (P), during occlusion (OCC), and at various times after reperfusion in control and nitrous oxide groups. *Significantly ($P < 0.05$) different from respective time point in the nitrous oxide group. LAD, left anterior descending coronary artery.

Systemic and coronary hemodynamics in nitrous oxide experiments are summarized in Table 2. Administration of 70% nitrous oxide produced significant ($P < 0.05$) increases in mean arterial pressure and left ventricular systolic pressure. The LAD coronary occlusion caused significant ($P < 0.05$) decreases

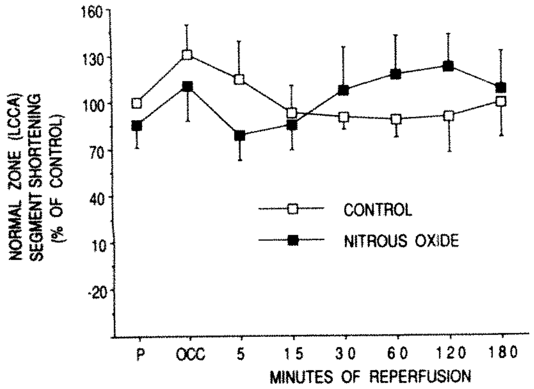

Figure 2. Normal zone segment shortening data (mean ± SE) before coronary artery occlusion (P), during occlusion (OCC), and at various times after reperfusion in control and nitrous oxide groups. LCCA, left circumflex coronary artery.

in heart rate, mean arterial pressure, left ventricular systolic pressure, rate-pressure product, and dP/dt from the 70% nitrous oxide state. A significant increase in left ventricular end-diastolic pressure was also observed during coronary artery occlusion. As was observed in the control experiments, a brief reactive hyperemia was noted immediately after LAD reperfusion in the presence of nitrous oxide; mean coronary blood flow in the LAD remained constant and not statistically different from the preocclusion levels during the remainder of the reperfusion period. Systolic shortening was replaced by paradoxical passive lengthening during coronary occlusion in the nitrous oxide group. In contrast to the control experiments, passive lengthening persisted during the first 30 min of reperfusion. In addition, the depression of regional contractile function observed in the LAD region after coronary reperfusion in nitrous oxide-treated dogs was significantly greater than that observed in the control experiments throughout reperfusion (Figure 1). As was observed in control experiments, no changes in segment shortening occurred in the normal (LCCA) region (Figure 2).

Regional myocardial perfusion assessed by radioactive microspheres before, during, and after coronary occlusion in both control and nitrous oxide experiments is summarized in Table 3. The LAD occlusion with diversion of retrograde flow produced severe reductions in blood flow to ischemic zone subepicardium, midmyocardium, and subendocardium. Total blood flow approached 0 $mL \cdot min^{-1} \cdot g^{-1}$ in the occluded vessel perfusion territory, indicating little if any coronary collateral flow to the ischemic zone. No changes in transmural perfusion were noted in the normal region in either group. Administration of nitrous oxide before coronary occlusion did not alter subepicardial, midmyocardial, and subendocardial perfusion when compared with preocclusion control in either the LAD or LCCA regions. As observed in control experiments, LAD occlusion resulted in transmural reduction in regional myocardial perfusion in the occluded vessel perfusion territory. No changes were observed in the normal region (LCCA). Reperfusion resulted in the return of myocardial blood flow to preocclusion levels in subendocardial, midmyocardial, and subepicardial regions of the LAD perfusion territory.

Discussion

Although nitrous oxide effects on myocardial function with normal coronary circulation have been well characterized, controversy remains as to its use in patients with ischemic heart disease. Philbin et al. (26) demonstrated in dogs that nitrous oxide added to an opioid-based anesthetic may produce contractile dysfunction (evaluated by appearance of postsystolic shortening) in myocardium perfused by a stenotic coronary artery. Ramsey et al. (27) confirmed these findings and demonstrated that the addition of nitrous oxide to halothane also resulted in global and regional contractile dysfunction in an identical model. Leone et al. (28) identified a dose-response relationship for this phenomenon and suggested that regional dysfunction in myocardium supplied by a critically narrowed coronary artery occurred when nitrous oxide was administered at inspired concentrations as low as 40%. Substitution of 50% nitrous oxide for 0.4% isoflurane produced a reduction in ventricular function and maldistribution of blood flow to ischemic myocardium in open-chest, acutely instrumented dogs in an investigation by Nathan (29). The same investigator (41) later reported that nitrous oxide effects on ischemic myocardium could be explained by systemic hemodynamic actions and direct depression of contractile function independent of direct coronary effects. Wilkowski et al. (30) demonstrated that 60% nitrous oxide produced significant constriction of epicardial coronary arteries assessed by angiography but did not alter coronary arteriolar tone, as evaluated by ^{133}Xe washout technique. The data suggested that nitrous oxide had differential effects on coronary vasculature, and these authors (30) speculated that epicardial coronary vasoconstriction produced by nitrous oxide may precipitate further blood supply decreases to myocardium distal to a stenosis. More recently, Pettis et al. (31) demonstrated in pigs that nitrous oxide produced epicardial coronary artery constriction in vivo by an endothelium-derived constricting-factor mechanism.

Although some evidence supports the contention that nitrous oxide may result in development of

Table 2. Hemodynamics During Coronary Artery Occlusion and Reperfusion in Nitrous Oxide Experiments in Dogs

	Preocclusion control	Preocclusion 70% N_2O	Coronary occlusion	Reperfusion (min)					
				5	15	30	60	120	180
HR (beats/min)	125 ± 9	124 ± 8	112 ± 3^{a,b}	110 ± 3^{a,b}	112 ± 4^{a,b}	112 ± 4^{a,b}	112 ± 6^{a,b}	114 ± 7^{a}	119 ± 6
MAP (mm Hg)	100 ± 8	114 ± 10^{a}	92 ± 9^{b}	85 ± 12^{a,b}	98 ± 7^{b}	99 ± 8^{b}	101 ± 9^{b}	97 ± 11^{b}	102 ± 9^{b}
LVSP (mm Hg)	124 ± 7	140 ± 10^{a}	115 ± 8^{b}	104 ± 11^{a,b}	118 ± 7^{b}	118 ± 8^{b}	121 ± 10	117 ± 11	120 ± 10
LVEDP (mm Hg)	4 ± 1	6 ± 1	10 ± 2^{a,b}	9 ± 2^{a,b}	9 ± 2^{a,b}	7 ± 2	6 ± 1	4 ± 1	5 ± 1
RPP (beats·min^{-1}·mm Hg × 10^3)	14.6 ± 1.2	16.4 ± 1.3	12.3 ± 1.2^{b}	10.9 ± 1.5^{a,b}	12.6 ± 0.9^{b}	12.7 ± 0.8^{b}	12.5 ± 0.8^{b}	12.4 ± 1.2^{b}	13.5 ± 1.4
dP/dt (mm Hg/s)	2000 ± 60	1950 ± 70	1610 ± 60^{a,b}	1410 ± 150^{a,b}	1580 ± 70^{a,b}	1620 ± 50^{a,b}	1670 ± 60^{a,b}	1760 ± 60^{a}	1790 ± 80^{a}
LAD MCBF (mL/min)	33 ± 4	36 ± 6	0 ± 0^{a,b}	52 ± 12^{a,b}	25 ± 6	25 ± 5	29 ± 7	27 ± 6	28 ± 6
LAD SS (%)	16.4 ± 1.8	14.4 ± 2.5	−2.8 ± 0.5^{a,b}	−1.4 ± 1.5^{a-c}	−1.6 ± 1.3^{a-c}	−2.4 ± 1.7^{a-c}	3.2 ± 1.6^{a-c}	3.1 ± 1.9^{a-c}	1.8 ± 2.6^{a-c}
LCCA SS (%)	11.3 ± 2.8	12.1 ± 3.2	11.5 ± 2.2	9.0 ± 2.6	9.4 ± 2.4	10.7 ± 1.9	11.9 ± 2.1	12.9 ± 2.6	10.9 ± 2.0

HR, heart rate; MAP, mean arterial pressure; LVSP, left ventricular systolic pressure; LVEDP, left ventricular end diastolic pressure; RPP, rate-pressure product; LAD, left anterior descending coronary artery; MCBF, mean coronary blood flow; SS, segment shortening; LCCA, left circumflex coronary artery.

Data are mean ± SE ($n = 7$).

[a] Significantly ($P < 0.05$) different from preocclusion control values.

[b] Significantly ($P < 0.05$) different from preocclusion 70% N_2O values.

[c] Significantly ($P < 0.05$) different from control experiments.

Table 3. Regional Myocardial Perfusion Before and After Coronary Artery Occlusion in Control and Nitrous Oxide Experiments in Dogs (mL·min^{-1}·g^{-1})

	Control experiments ($n = 7$)			Nitrous oxide experiments ($n = 7$)			
	Preocclusion	Occlusion	Reperfusion	Preocclusion	70% N_2O	Occlusion	Reperfusion
Ischemic LAD region							
Subepicardium	0.96 ± 0.19	0.05 ± 0.02^{a}	0.84 ± 0.24	0.84 ± 0.11	0.95 ± 0.21	0.08 ± 0.03^{a,b}	0.84 ± 0.17
Midmyocardium	0.96 ± 0.19	0.04 ± 0.02^{a}	0.72 ± 0.16	0.81 ± 0.09	0.86 ± 0.17	0.05 ± 0.02^{a,b}	0.56 ± 0.05
Subendocardium	0.97 ± 0.17	0.04 ± 0.02^{a}	0.72 ± 0.18	0.89 ± 0.10	1.03 ± 0.18	0.03 ± 0.03^{a,b}	0.64 ± 0.08
Transmural	1.12 ± 0.12	0.07 ± 0.03^{a}	0.87 ± 0.13	0.85 ± 0.10	0.95 ± 0.18	0.05 ± 0.03^{a,b}	0.68 ± 0.10
Endo/epi	1.20 ± 0.15	0.32 ± 0.22^{a}	0.83 ± 0.22	1.09 ± 0.09	1.15 ± 0.08	0.52 ± 0.26^{a,b}	0.84 ± 0.08
Normal LCCA region							
Subepicardium	0.75 ± 0.09	0.61 ± 0.09	0.81 ± 0.22	0.96 ± 0.13	0.92 ± 0.14	0.81 ± 0.09	0.75 ± 0.08
Midmyocardium	0.87 ± 0.18	0.75 ± 0.08	1.04 ± 0.36	0.93 ± 0.11	1.02 ± 0.16	0.87 ± 0.10	0.79 ± 0.09
Subendocardium	1.12 ± 0.25	0.85 ± 0.15	1.05 ± 0.31	1.20 ± 0.13	1.17 ± 0.17	0.97 ± 0.07	0.89 ± 0.11^{a}
Transmural	0.91 ± 0.17	0.74 ± 0.10	0.90 ± 0.23	1.03 ± 0.12	1.04 ± 0.15	0.88 ± 0.08	0.81 ± 0.09
Endo/epi	1.44 ± 0.16	1.39 ± 0.10	1.25 ± 0.05	1.30 ± 0.11	1.29 ± 0.08	1.26 ± 0.11	1.20 ± 0.10

LAD, left anterior descending coronary artery; Endo/epi, ratio of subendocardial to subepicardial perfusion; LCCA, left circumflex coronary artery.

Data are mean ± SE.

[a] Significantly ($P < 0.05$) different from preocclusion values.

[b] Significantly ($P < 0.05$) different from 70% N_2O values.

myocardial ischemia in experimental models of coronary disease, clinical studies examining the effects of nitrous oxide in patients with ischemic heart disease have not verified this conclusion. Nitrous oxide has been shown to decrease myocardial contractility when administered alone (32,33) or in combination with opioids (34,35) to patients with coronary artery disease, but no evidence of new ischemia occurred, indirectly suggesting that nitrous oxide was not producing clinically significant effects. Using more specific ischemia indicators, others have shown that nitrous oxide added to another anesthetic does not precipitate myocardial ischemia in susceptible patients. Cahalan et al. (36) examined ST segment changes and segmental left ventricular function with either nitrous oxide or nitrogen in patients undergoing coronary bypass graft surgery. No ST segment alterations or regional wall motion abnormalities were observed with the introduction of nitrous oxide, suggesting that it did not produce myocardial ischemia when used with fentanyl during anesthesia. Mitchell et al. (37) performed a similar study in patients with coronary artery disease and impaired left ventricular function. These investigators found that nitrous oxide did not cause clinically detectable ischemia and did not exacerbate global left ventricular dysfunction (37). Regional wall motion abnormalities evaluated by two-dimensional transesophageal echocardiography in patients anesthetized with sufentanil for coronary bypass surgery before cardiopulmonary bypass were also not detected during exposure to 70% nitrous oxide when compared with 70% nitrogen (38). Thus, although some evidence exists to suggest that nitrous oxide may contribute to regional contractile dysfunction in experimental models of coronary artery obstruction, these concerns have not been clinically demonstrated.

Persistent regional contractile dysfunction after blood flow has been restored to transiently ischemic myocardium has been extensively characterized (1–6,10). Spontaneous coronary artery reperfusion after thrombus formation or spasm is a clinically recognized phenomenon that occurs frequently in patients with coronary artery disease. This dynamic process represents an important part of the natural history of coronary artery disease. Interventions, such as thrombolytic therapy, angioplasty, or coronary artery bypass graft surgery, used to reestablish coronary blood flow in the management of acute ischemia may also be associated with development of stunned myocardium. Although the magnitude of postischemic dysfunction is primarily determined by duration and severity of ischemic insult (1,4,5), ischemia and subsequent reperfusion produce a cascade of events possibly responsible for subsequent reperfusion injury (6,7).

Although a number of potential mechanisms have been suggested, the etiology of contractile dysfunction in postischemic, reperfused myocardium remains unclear. Several studies (9–11,42) have shown that high-energy phosphate levels are depressed and recover in a time-course that parallels the functional recovery of stunned myocardium. The assertion that inadequate postischemic adenosine triphosphate levels are responsible for the slow recovery of regional contractile function is not without controversy (16,43–45). Production of oxygen-derived free radicals, either by ischemic myocytes or by infiltrating neutrophils with reperfusion-supplied oxygen, may be important mediators in the production of postischemic contractile dysfunction (12,13,46–48). Other factors, including intracellular calcium overload (8,43,49), myocyte excitation-contraction uncoupling (14), abnormalities in cardiac sympathetic neural responsiveness (50), and myocyte edema (51), have also been implicated.

Pharmacologic interventions directed toward improvement of postischemic, reperfused myocardial performance have focused on modulation of these abnormalities. Calcium channel antagonists significantly enhance functional recovery of stunned myocardium by controlling elevations of intracellular calcium and by reducing myocardial oxygen demand and decreasing severity of ischemia during coronary artery occlusion (15–18). Scavenging of oxygen-derived free radicals with superoxide dismutase and catalase enhances the recovery of stunned myocardium (22). Decreased myocardial oxygen consumption during the ischemic event induced by β-adrenergic antagonists (20), specific bradycardic agents (21), and vasodilators (15,19) may reduce high-energy phosphate catabolism and lead to more rapid recovery of contractile function. More recently, a monoclonal antibody directed against a neutrophil-derived adhesion protein was effective in improving functional outcome after brief myocardial ischemia (47), providing a potential immunologic treatment option, and emphasizing that neutrophil migration and activation (48) may also play a critical role in the development of reperfusion-induced contractile dysfunction.

The actions of volatile anesthetics on stunned myocardium recovery have recently been examined. Freedman et al. (24) reported that enflurane improved functional recovery of stunned myocardium in isolated rat hearts. An investigation from this laboratory (23) demonstrated that recovery of contractile function of postischemic, reperfused myocardium is enhanced by halothane or isoflurane when these agents are administered to chronically instrumented dogs before or during 15 min of total coronary artery occlusion. This protective effect of inhaled anesthetics was attributed to improvement in the oxygen supply-demand balance, coupled with calcium influx blockade by voltage-dependent slow channels (52,53) and stimulation of calcium uptake into the sarcoplasmic reticulum (54,55). Administration of halothane and isoflurane during reperfusion rather than before and during ischemia did not enhance function recovery of stunned myocardium when these volatile anesthetics were delivered (25).

The present investigation indicates that 70% nitrous oxide impairs functional recovery of postischemic, reperfused myocardium compared with 70% nitrogen control. Administration of nitrous oxide before and during coronary occlusion led to significantly greater mortality secondary to ventricular fibrillation. The mechanisms by which nitrous oxide depressed recovery of stunned myocardium and increased mortality are unknown. Before occlusion, nitrous oxide increased mean arterial and left ventricular systolic pressures. The rate-pressure product, an indirect indicator of myocardial oxygen demand, numerically increased, although this change did not reach statistical significance. Although myocardial oxygen consumption was not specifically measured, these alterations indirectly suggest that a greater imbalance in the myocardial oxygen supply-demand relationship may represent a potential mechanism by which nitrous oxide increases ischemia severity during coronary occlusion, thereby reducing recovery of function. Sympathetic nerve stimulation (56) and increased norepinephrine release (57) during nitrous oxide may have contributed to this process, although serum catecholamines were not specifically obtained in the present investigation. Nitrous oxide produces direct negative inotropic effects in vivo (58) and in vitro (59). Depression of myocardial contractility should improve functional recovery of stunned myocardium by decreasing myocardial oxygen consumption during the ischemic episode. However, nitrous oxide-induced sympathetic nervous system stimulation may mask these direct reductions in contractile function (60) and therefore negate possible protective effects of direct decreases in contractility. Reductive metabolism of nitrous oxide to free radical intermediates in certain anaerobic environments could represent a theoretical mechanism by which this agent may impair functional recovery of postischemic, reperfused myocardium (61). Constriction of epicardial coronary arteries, possibly mediated by increased sympathetic tone during nitrous oxide, could also decrease myocardial oxygen supply (30,31). Although epicardial coronary artery diameter was not specifically measured in the present study, there were no changes in transmural coronary blood flow assessed by radiolabeled microspheres in either ischemic or nonischemic zones with nitrous oxide, suggesting that intramyocardial blood flow alterations were not responsible for differences observed in the functional recovery of stunned myocardium.

Barbiturate anesthesia used in this investigation is commonly used in open-chest dog preparations and offers the advantage of hemodynamic stability over a prolonged time-course without the requirement of repeated dosing or anesthetic adjuvants. In addition, the time-course of functional recovery of postischemic, reperfused myocardium is similar in conscious and barbiturate-anesthetized dogs despite significantly different systemic hemodynamic profiles (62). In contrast, volatile anesthetics significantly enhance the functional recovery of stunned myocardium (23,24), a finding that may complicate interpretation of the effects of nitrous oxide on postischemic reperfusion injury. Clearly, however, the use of a pure barbiturate anesthetic in the absence of opioids or other anesthetic adjuvants is useful only for an experimental preparation, and results of this investigation must be interpreted within the constraints of this anesthetic regimen.

In summary, 70% nitrous oxide significantly reduced functional recovery of postischemic, reperfused myocardium and resulted in significantly greater mortality when compared with 70% nitrogen in barbiturate-anesthetized, open-chest dogs. Extension of the findings of this investigation to clinical settings should be approached with caution. The results indicate that the time-course of recovery of stunned myocardium is further delayed by nitrous oxide.

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Fertilization and Mouse Embryo Development in the Presence of Midazolam

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Mouse embryo in vitro development elucidates the effect of a pharmacologic agent on cellular differentiation. Midazolam provides conscious sedation for patients undergoing egg retrieval for in vitro fertilization and is found in patient follicular fluid. Mouse preimplantation embryo formation and development were evaluated in the presence of midazolam. Midazolam was cocultured with two-cell mouse preimplantation embryos over 72 h and injected systemically just before ovulation and coitus. Concentrations to 12.5 μg/mL displayed no significant toxic effects on in vitro two-cell-to-blastocyst development. Doses to 35.0 mg/kg did not prevent or impair in vivo fertilization. Midazolam has no adverse effect on in vitro development of two-cell-to-blastocyst-stage embryos nor on in vivo fertilization and cell division at concentrations approximating and exceeding those that ova are exposed to during clinical anesthesia. Midazolam is recommended for use to induce sedation in human in vitro fertilization where association with gametes and zygotes is probable.

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Mouse embryo culturing was initiated in the Embryonics Laboratory at Old Dominion University in 1980 as a quality-control screening assay for media, supplements, culture ware, and related equipment used in developing the human in vitro fertilization program in Norfolk, Virginia (1–5). The mouse system was used to screen potential toxic effects of anesthetics used in egg retrieval for in vitro fertilization (IVF). Midazolam doses of 0.070–0.080 mg/kg were used for intravenous induction of anesthesia in IVF. We administered a total of approximately 0.07 mg/kg of midazolam to seven patients who were undergoing egg retrieval. Midazolam concentrations ranging from 17.7 to <1 ng/mL were found in follicular fluid samples after ova retrieval from the seven patients (unpublished data). Eggs from all seven patients fertilized at a rate of 94% (29/31); there were two of seven (29%) biochemical pregnancies, and of those two, one of seven (14%) term pregnancies (unpublished data). For this sample size, fertilization and pregnancy rates are within acceptable limits. Research into the potential toxic effects of midazolam was prompted by these observations. Mouse zygote formation and early preembryo development were used as a model to test midazolam.

Methods

Mice

The experimental protocol was submitted and approved by the University Animal Use and Care Committee. Embryos used in this study were obtained from hybrid B_6CBA F_1 ($C57Bl_6 \times CBA$) virgin female mice (purchased from the Jackson Laboratory, Bar Harbor, Me.) crossed with outbred CD-1 males 3–10 mo old (Charles River Laboratories, Wilmington, Del.). Unlike many strains, this F_2 hybrid mouse strain has proved to produce consistently high numbers of embryos with 100% development to the blastula stage in 72 h if all culturing variables are at an optimum (3). Mice were 4–6 wk old when received and acclimated to our animal facility before use. All mice were used within 12 wk of purchase. Mice were maintained on a lighting regime of 14 h light, 10 h dark (lights on at 5 AM) at 21°–24°C and were given laboratory rodent chow (Ralston Purina, St. Louis, Mo.) and water ad libitum. Euthanasia was by cervical dislocation, approved by the Panel on Euthanasia of the American Veterinary Medical Association.

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Superovulation and Mating

Female mice selected at random with regard to estrous were induced to superovulate by intraperitoneal (IP) injections of 5 IU of pregnant mare serum gonadotropin (Sigma Chemical Co., St. Louis, Mo.) followed 48 h later by 5 IU of human chorionic gonadotropin (hCG) (Sigma). At hCG injection time, each female mouse was placed in a cage with one proved fertile male CD-1 mouse. Both injections were given between 4 and 6 PM. Female mice go into estrous and mate within 6 h after hCG injection, with ovulation occurring between 10 and 13 h after hCG injection. Between 9 and 10 AM on the following morning, female mice were inspected for vaginal plugs and the results of the males' copulatory performances were recorded. Any male failing to produce a copulation plug after more than three consecutive weeks was culled from the colony.

Collection of Embryos

Plug-positive females were sequentially killed by cervical dislocation over a period of 2 h starting approximately 42 h after the hCG injection. The abdomen of the mouse cadaver was entered by tearing a small hole over the umbilicus and then stripping the skin simultaneously down over the hindlegs and up over the forelegs. This technique leaves a completely sterile field without any mouse hair and obviates the use of antiseptic agents that can compromise embryo viability. The rectus abdominis was severed 2–3 mm superior to the symphysis pubis, continuing the incision bilaterally up each flank to the ribs. Oviducts were excised by first gently stretching/tearing the mesosalpinx and mesometrium close to each oviduct and uterine horn, respectively, and then cutting between the oviduct and ovary at the intramural junction with microsurgical scissors (No. ST-SAS-15, ASSI, Accurate Scientific & Surgical Instruments, Westbury, N.Y.). Three pairs of oviducts were placed in each sterile 35 × 10-mm polystyrene Nunclon culture dish (Thomas Scientific, Swedesboro, N.J.) containing 2 mL of modified Krebs-Ringer-bicarbonate (mKRB) medium. Under a Ziess dissecting stereomicroscope (Eastern Microscope Co., Raleigh, N.C.) at 20× magnification, watchmaker forceps (ASSI, No. ST-JFC-7) were used to slide the swollen infundibulum onto a 30-gauge (B-D, Becton Dickinson, Baxter Diagnostics Inc., Scientific Products Division, Columbia, Md.) sterile needle attached to a 1-mL sterile syringe (B-D). Embryos were washed from the oviducts with medium lightly expressed from the syringe. Groups of five normal (judged by oval, bilateral symmetry of the two blastomeres with narrow perivitelline space and presence of two small polar bodies) two-cell embryos were evaluated at 32× magnification and collected from the petri dish with a 10-μL Eppendorf (Microliter Pipetters, Fisher Scientific, Norcross, Ga.) micropipette fitted with a sterile tip and dispensed into flat-sided culture tubes containing 1.0 mL of medium per tube (110 × 16-mm Nunclon flat-sided, screw-top tissue culture tubes, Thomas Scientific). At least five embryos from each mouse were cultured in a tube containing control medium. Each test medium was evaluated in triplicate cultures.

Media

Media used was mKRB solution supplemented with 4 mg bovine serum albumin per milliliter (1). After composition, media was checked for a pH value between 7.6 and 7.8 (before CO_2 equilibration); filter-sterilized into 150-mL, red-necked, 0.22-μm filter units (type TC, Nalge Company, Division of Sybron Corp., Rochester, N.Y.), dispensed into the tissue culture tubes, and incubated at 37°C in 5% CO_2 in air for at least 18 h before use.

Midazolam

Midazolam HCl is commercially available as injectable Versed in 1-mL vials at 5 mg/mL or 5-mL vials at 1 mg/mL (Roche Products Inc., Nutley, N.J.). These vials contain the preservatives 0.01% disodium edetate and 1% benzyl alcohol in 0.8% aqueous NaCl. To facilitate dosage titration and minimize the preservative concentration, the 1-mL vial (5 mg/mL) of midazolam HCl was preferentially used.

In vitro response of embryo development to midazolam. Two-cell embryos were directly exposed to midazolam to determine the lowest dose completely inhibiting development to morula-plus-blastocyst stage after 72 h in culture. Subsequently, two-cell embryos were exposed to concentrations of midazolam below this lowest dose determined to totally inhibit development to morula or beyond.

Starting from 5-mg/mL concentrations of midazolam, solutions were prepared by dilution in mKRB medium to final concentrations of 500,000, 50,000, 25,000, 12,500, 5000, 500, 50, 25, 10, and 5 ng/mL. Use of the 5-mg/mL vial for making the most concentrated solutions results in 10 μL of Versed placed in 1 mL of mKRB medium. Therefore, in the most concentrated tube (500 μg/mL) of incubation medium, two-cell embryos would experience a final concentration of 0.0001% disodium edetate (1 μg/mL) and 0.01% benzyl alcohol (0.1 μL/mL) preservatives.

Table 1. Effects of Midazolam on the 72-h Culture of Two-Cell Mouse Embryos[a]

			Embryo stage					
Treatment	Midazolam (ng/mL)	Total two-cell embryos cultured	2 Cell	3–4 Cell	6–8 Cell	16–36 Cell	Morula + blastocyst	Degenerating embryos
A	50,000	75	43 (60.0%)	4 (5.3%)	16 (21.3%)	0 (0.0%)	0 (0.0%)	12 (16.3%)
B	25,000	46	6 (13.0%)	19 (41.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	21 (45.0%)
C	12,500	31	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	26 (83.8%)	5 (16.0%)
D	5,000	59	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	53 (88.3%)	5 (16.0%)
E	500	38	0 (0.0%)	0 (0.0%)	2 (5.2%)	0 (0.0%)	33 (87.0%)	3 (7.9%)
F	50	30	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	28 (93.0%)	1 (3.3%)
G	25	30	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	29 (97.0%)	0 (0.0%)
H	10	30	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	28 (93.0%)	1 (3.3%)
I	5	33	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	32 (97.0%)	1 (3.3%)
	Control	37	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	36 (97.0%)	1 (3.3%)

[a] Two-cell embryos were coincubated in varying concentrations of midazolam to determine the lowest dose inhibiting development to morula-plus-blastocyst stages. Two-cell embryos were subsequently exposed to doses of midazolam below the minimal inhibitory dose. One-factor fixed-effects randomized block analysis of variation analysis of morula-plus-blastocyst development at 72 h in culture presented significant difference in higher concentrations (50,000 and 25,000 ng/mL) at $P < 0.005$ level. Lower concentrations allowed development. Furthermore, there were significant differences among treatments. Treatment A was equal to B. Treatments C, D, E, F, G, H, I, were equal and different from A.

Doses of midazolam inhibiting fertilization in vivo. Female mice were given an intraperitoneal injection of midazolam during the superovulation protocol immediately before the hCG injection. Midazolam doses for the mice were calculated from an equivalent dose administered during human ova harvesting: 0.070–0.080 mg/kg. Not only was an equivalent concentration used, but injections 5 (0.35 mg/kg), 40 (2.8 mg/kg), 100 (7.0 mg/kg), 200 (14.0 mg/kg), and 500 (35.0 mg/kg) times greater were given. Each midazolam solution, calculated for a 24-g mouse (weight ranged from 23 to 25 g), was administered in a constant volume of 0.1 mL. In the most concentrated intraperitoneal dose (35 mg/kg), a single mouse would receive approximately 100 ng of disodium edetate and 10 μL of benzyl alcohol.

Each female was placed with one male and checked within 12 h for a vaginal copulation plug. Approximately 42 h after hCG injection, two-cell embryos were collected. The presence of gametes or single-cell embryos, with absence of two-cell or later embryos, would indicate a midazolam-induced blocking or retardation of fertilization. Normal two-cell mouse embryos were collected if fertilization was not blocked or retarded and placed into culture media to observe normal development after 48 and 72 h.

Statistical Analysis

Development of two-cell mouse embryos to morula-plus-blastocyst stages after 72 h in culture was evaluated in both in vitro and in vivo experiments for (a) effect of midazolam in culture medium on embryo development and (b) effect of in vivo injection of midazolam into the female on embryo production and development. Data (Tables 1 and 2) were evaluated in a one-factor fixed-effects randomized block analysis of variance to test for overall significance among treatments, followed by Tukey's HSD (honestly significant difference) test to evaluate differences between specific treatments.

Results

Development of Two-Cell Mouse Embryo in Midazolam

Recovered two-cell mouse embryos were observed for development at 48 and 72 h. Various concentrations of midazolam were used in culture media, and their effects on embryo development after 72 h have been summarized in Table 1. One-hundred percent inhibition of morula-plus-blastocyst stage occurred with the two highest midazolam concentrations (50,000 and 25,000 ng/mL), but initial growth and cleavage beyond the two-cell stage was quantitatively different between these two concentrations. Sixty percent of the embryos were arrested at the two-cell stage with 50,000 ng/mL, whereas only 13% of the embryos were arrested at the two-cell stage with 25,000 ng/mL. Concentrations of midazolam ≤12,500 ng/mL did not display any significant toxic effects on morula-plus-blastocyst development (Table 1), with this development being >84% in all groups; however, there was an observable trend of reduced development in the 12,500–500-ng range (83%–88% morula-plus-blastocyst development). Control cultures of two-cell mouse embryos show a morula-plus-blastocyst development of 97% after 72 h in culture.

Table 2. In Vitro Two-Cell Mouse Embryo Development From Midazolam-Injected Dams

Midazolam dose (mg/kg)[a]	Total two-cell embryos recovered	Embryo stage					Degenerating cells
		2 Cell	3–4 Cell	6–8 Cell	16–32 Cell	Morula + blastocyst	
0.070	93	0	0	0	0	91 (97.8%)	2 (2.2%)
0.350	92	0	0	3 (3.2%)	9 (9.8%)	69 (74.2%)	11 (12.0%)
2.80	98	0	2 (2.0%)	0	2 (2.0%)	87 (89.0%	7 (7.2%)
7.0	104	5 (4.8%)	0	0	2 (2.0%)	92 (88.4%)	5 (4.8%)
14.0	72	0	0	0	0	71 (98.6%)	1 (1.3%)
35.0	95	0	0	0	0	93 (97.8%)	2 (2.1%)

Female mice were injected intraperitoneally with midazolam 48 h after pregnant mare serum gonadotropin and immediately before human chorionic gonadotropin injections. Two-cell embryos were observed for development at 72 h culture. One-factor fixed-effects randomized block analysis of variance analysis of two-cell mouse embryos development to morula-plus-blastocyst stage at 72 h in culture did not differ among treatments.

[a] Administered in a constant volume of 0.1 mL.

To arrive at a comparative midazolam toxicity value, percents were summed for embryos (a) demonstrating degeneration or fragmentation and (b) arrested at the two-cell stage after 72 h in culture. Midazolam concentrations of 50,000 ng/mL resulted in a toxic value of 76%, whereas concentrations of 25,000 ng/mL resulted in a toxic value of 58%.

In Vivo Fertilization After Midazolam Injection Into the Dam

Doses up to 500 times the human baseline dose produced no evidence that midazolam prevented or impaired in vivo fertilization. Normal two-cell mouse embryos were collected approximately 42 h after in vivo injection of midazolam in hCG (approximately 36 h after coitus). Development proceeded to control level percent of morula-plus-blastocyst stage after 72 h in culture (Table 2).

In several experiments, a low number of three- and four-cell embryos were collected along with two-cell embryos 42 h after midazolam and hCG injection. In comparison, control mice injected with pregnant mare serum gonadotropin and hCG rarely produced anything but two-cell embryos by this time.

Discussion

The in vitro culture of in vivo fertilized two-cell mouse embryos has been used routinely over the past 10 yr as a quality control of media and supplements of the Human IVF Program in Norfolk. One of the driving forces behind the use of the mouse embryo quality control has been the need to determine potential toxic effects of substances in contact with the human egg or culture media during egg retrieval and the in vitro fertilization process. Detection of midazolam in follicular fluid during human egg retrieval in the Norfolk Human IVF Program prompted this study. To rule out adverse effects of this anesthetic drug, mouse preimplantation embryos were fertilized and subsequently cultured in the presence of midazolam.

Results reported in this study came from two sets of experiments. In the first set, two-cell mouse embryos were cocultured in increasing concentrations of midazolam while their development was monitored. The Norfolk Human IVF Program washes the retrieved eggs twice and then places the ova in 3 mL of fresh media with 5 × 10^4 sperm/mL. Total time of midazolam exposure would never exceed 60 min, and in the seven cases where follicular fluid was studied, the concentration never exceeded 20 ng/mL. In these experiments, 72-h embryo coculture with midazolam without embryo washing exposed embryos to incremental concentrations of midazolam bracketing as well as exceeding that found in follicular fluids and also exceeding the time of exposure to this anesthetic. Midazolam did not produce any inhibitory effects on embryo development up to and including a concentration of 12,500 ng/mL (Table 1). A 0-ng/mL midazolam control was deemed trivial after initial pilot experiments showed no effect on embryo development at lowest doses. However, finding the level of disodium edetate and benzyl alcohol that arrests mouse embryo development to ensure that the effect observed at the higher doses was due to midazolam and not the preservative would have value. This work remains to be done.

The second set of experiments imitated the condition of human ova exposure to midazolam in follicular fluids during egg retrieval. Midazolam is a lipid-soluble drug that should be able to penetrate peritoneal membranes, follicular walls, and the unharvested ova. In this experiment, midazolam injected intraperitoneally into mice immediately before hCG injection (10–13 h before ovulation) did not impair fertilization. After intraperitoneal administration, midazolam in the ovary would undoubtedly achieve a lesser acme and have a more prolonged duration than the titration curve for ovarian midazolam after intravenous injection. Although achievable, tail vein injections in the mouse require either (a) pretranquilizing, which would be a confounding factor in testing midazolam, or (b) physical restraint with resultant large releases of thyroid-stimulating hormone and adrenocorticotropic hormone, which would have such wide ranging effects that variables and conclusions might be difficult to determine. Furthermore, absolute ovarian midazolam concentrations did not merit the challenge of discovery, but the goal was to establish the range within which midazolam would exert deleterious consequences. Midazolam was injected in incremental doses to determine the minimal inhibitory dose on in vivo fertilization. Doses up to 500-fold normal did not inhibit fertilization (Table 2) but were lethal in some cases. Significantly, in both sets of experiments, midazolam appeared to actually accelerate embryo development rather than inhibit it. In some experimental trials, blastocysts were observed after 48 h of growth in midazolam, compared with only morulae observed in control cultures. In dams injected with midazolam, collections of three- and four-cell embryos were often observed along with two-cell embryos, whereas control mice produced only two-cell embryos (unanalyzed observation). The embryo exists only on inherited material up to the mid-two-cell stage; many of the embryonic genes are switched on some time after the mid-two-cell stage (6). These observations suggested the possibility that the mitogenic activity of midazolam may increase DNA replication or translation. Excess storage of proteins and large numbers of copies of rRNA could account for the accelerated effect observed during the early cleavages of the embryos. Further studies will be necessary to determine the exact mechanism of midazolam action at the molecular level.

These experiments did not include studying the effects of midazolam on in vitro fertilization; however, because no inhibition was forthcoming on in vivo embryo production with overwhelming intraperitoneal doses, it seems valid to assume no effect of midazolam on in vitro fertilization. Nevertheless, it could be argued that the in vivo study of fertilization as described in this experiment may not reflect actual exposure to midazolam in follicles at a critical time in the maturation period of the ovum when it proceeds from prophase I to metaphase II, because the half-life of midazolam in the terminal elimination phase averages 1–4 h (7). In addition, although it has been assumed that serum concentrations of midazolam reflect follicular concentrations of midazolam, no direct measurement of midazolam in follicular fluid was performed in the mouse. Because the lipophilic nature of midazolam, and the fact that it was measured in human follicular fluid in the Norfolk Human IVF Program, a strong case exists for assuming its presence in the mouse follicle.

The mouse embryo system has advantages over the sea urchin for studying the mammalian fertilization process and embryo development. Effects of fentanyl on fertilization and early development of Echinodermata eggs were published by Bruce et al. in 1985. They reported that fentanyl in doses 7 and 14 times greater than the normal human dose did not inhibit fertilization in the sea urchin (8). Sea urchin division after fertilization is rapid, and a free-swimming, ciliated blastula results within 12 h. The process normally occurs in somewhat inconstant open seawater in a visible environment (8). In contrast, the mouse embryo divides slowly after fertilization, moving along the oviduct into the uterus for implantation 4.5 days after fertilization, all of which normally occurs in the highly constant and hidden in vivo environment. Despite this slower embryonic development, use of the mouse system permits an understanding of how genes control the growth and differentiation of the mammalian embryo (9). The mouse embryo system should be preferentially used for the screening of drugs. These experiments show that a drug can readily be tested for its effects on fertilization and embryo development.

In conclusion, these results indicate that recommended doses of midazolam have no inhibitory effects on fertilization and consequent embryo development to the blastocyst stage in mouse embryos. Clinical implications of these results reduce the uncertainty of potential inhibitory effects of midazolam during human egg retrieval. This study is the first to report the use of the mouse embryo system to evaluate the effects of anesthetic drugs on fertilization and early embryo development. Further expansion of these tests could include in vitro as well as in vivo fertilization, embryo transfer to surrogate females, implantation and placentation, and live birth. Longitudinal studies could give information on birth defects in second and third generations.

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Skin Pretreatments for Shortening Onset of Dermal Patch Anesthesia With 3% GA MHPh 2Na–10% Lidocaine Gel Mixture

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Three types of skin pretreatments (stripping with adhesive tape, scrubbing with Skin-Pure jelly, and cleaning with benzine) were studied in 21 volunteers to determine whether the pretreatments could shorten the application period of transdermal 3% GA MHPh 2Na–10% lidocaine gel. Before application of the gel, each subject received skin pretreatment on the volar surface of one forearm. Then, the lidocaine gel soaked in a round sponge was applied on both the pretreated area of the forearm and the unpretreated contrast area of the other forearm. A pain score was obtained from each subject at 30, 45, 60, and 75 min after placement of the dermal patch by noting the number of painful pinpricks of five delivered. The mean pain scores on the pretreated side were significantly lower at 30, 45, and 60 min in the stripping study group and at 45 and 60 min in the cleaning study group, compared with the corresponding scores on the unpretreated side ($P < 0.05$). Skin pretreatments, such as stripping and cleaning, are useful for shortening the onset of the dermal patch anesthesia.

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We have developed a transdermally applicable 10% lidocaine gel mixture with 3% glycyrrhetinic acid monohemiphthalate disodium (GA MHPh 2Na) as an absorption promoter (1). A minimal 60-min application of 3% GA MHPh 2Na–10% lidocaine gel under occlusion was required to reduce a pinprick pain score <20% (1,2). Ideal dermal patch anesthesia should be more rapid in onset. Because the stratum corneum is thought to be the main barrier to the absorption of the gel through the skin, skin pretreatments that attenuate the barrier effect could shorten the application period of the gel.

The present study describes the effects of three types of skin pretreatments on the onset of dermal patch anesthesia.

Methods

After approval from the Institutional Ethics Committee on Human Research, we studied 21 healthy adult volunteers (all male, median age 31 yr, range 22–47 yr). According to the skin pretreatment to be given, the subjects were randomly allocated to one of the following three study groups: stripping ($n = 7$), scrubbing ($n = 7$), or cleaning ($n = 7$). Predictable effects of the skin pretreatments were not told to the subjects.

Both forearms were used to evaluate the effects of the skin pretreatments. Before the transdermal application of 3% GA MHPh 2Na–10% lidocaine gel, each subject received the skin pretreatment on the volar surface approximately 10 cm below the anterior cubital fossa of the left or the right forearm. In the stripping study group, 10 pieces of adhesive tape were placed on the skin and removed successively on the same area. In the scrubbing study group, approximately 1 g of Skin-Pure jelly (Nihon Koden, Japan), which is designed for electrode site cleaning to enhance stable electrocardiographic monitoring and recording by reducing electrode-to-skin impedance, was applied to the skin, and the area was scrubbed 10 times with a dry gauze pad. Then, the skin area was wiped dry of the jelly with a soft tissue. The formula of the Skin-Pure jelly was not revealed, because it was under application for a patent. In the cleaning

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Table 1. Pinprick Pain Scores on the Pretreated and Unpretreated Forearm Sides After Initiation of Dermal Patch Anesthesia in the Three Study Groups

	Stripping group (*n* = 7)		Scrubbing group (*n* = 7)		Cleaning group (*n* = 7)	
	PT side	unPT side	PT side	unPT side	PT side	unPT side
0 min	5.0 ± 0.0	5.0 ± 0.0	5.0 ± 0.0	5.0 ± 0.0	5.0 ± 0.0	5.0 ± 0.0
30 min	0.8 ± 0.8[a]	2.8 ± 1.3	3.0 ± 1.2	3.3 ± 1.6	2.8 ± 1.9	3.4 ± 1.5
45 min	0.5 ± 0.6[a]	2.0 ± 0.9	1.9 ± 0.8	2.1 ± 1.3	1.0 ± 1.9[a]	2.0 ± 2.2
60 min	0.0 ± 0.0[a]	0.8 ± 1.0	0.1 ± 0.4	0.2 ± 0.4	0.3 ± 0.5[a]	1.6 ± 1.5
75 min	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.1 ± 0.2	0.2 ± 0.3	0.3 ± 0.4

PT, pretreated; unPT, unpretreated.
Results are presented as mean ± SD.
[a] Significantly lower compared with the unpretreated side ($P < 0.05$).

study group, the skin area was wiped 10 times with a gauze pad containing benzine, which is a purified distillate from petroleum consisting of hydrocarbons chiefly of the methane series and is used as a solvent for organic compounds.

Then, approximately 0.3 g of the lidocaine gel soaked in a round sponge (25 mm in diameter and 1 mm thick) was applied to both the pretreated area of one forearm and the contrast unpretreated area of the other forearm and was kept covered with adhesive plastic film (Tegaderm, 3M Corp.) for 75 min. The composition of the 3% GA MHPh 2Na–10% lidocaine gel mixture is described elsewhere (1–3).

The accelerative effect of each pretreatment on the transdermal gel absorption was evaluated by comparing the analgesic effects of the gel on the forearms with and without the pretreatments. The analgesic effect was assessed with the pinprick method at 30, 45, 60, and 75 min after placement of the dermal patch by an experienced anesthesiologist who was not involved in administering the patches nor informed about the skin treatments. The cover was temporarily lifted and the sponge pulled to one side during the assessment. The gel-treated skin area was pricked five times with a disposable 26-gauge sterile needle to determine the presence or absence of pain sensation. A pain score was obtained from each subject by noting the number of painful pinpricks of the five delivered. When a pinprick induced some pain, although attenuated, it was counted as 0.5.

Statistical analysis was performed with a Wilcoxon *t*-test for comparison between pain scores on the pretreated and the unpretreated side. Values of $P < 0.05$ were considered significant.

Results

In the stripping study group, the mean pinprick pain score at 30 min (30-min pain score) was as low as 0.8 ± 0.8 (mean ± SD) on the pretreated side. The 30-, 45-, and 60-min pain scores on the pretreated side were significantly lower than the corresponding pain scores on the unpretreated side ($P < 0.05$) (Table 1, Figure 1).

In the scrubbing study group, the 30- and 45-min pain scores on the pretreated side were lower than

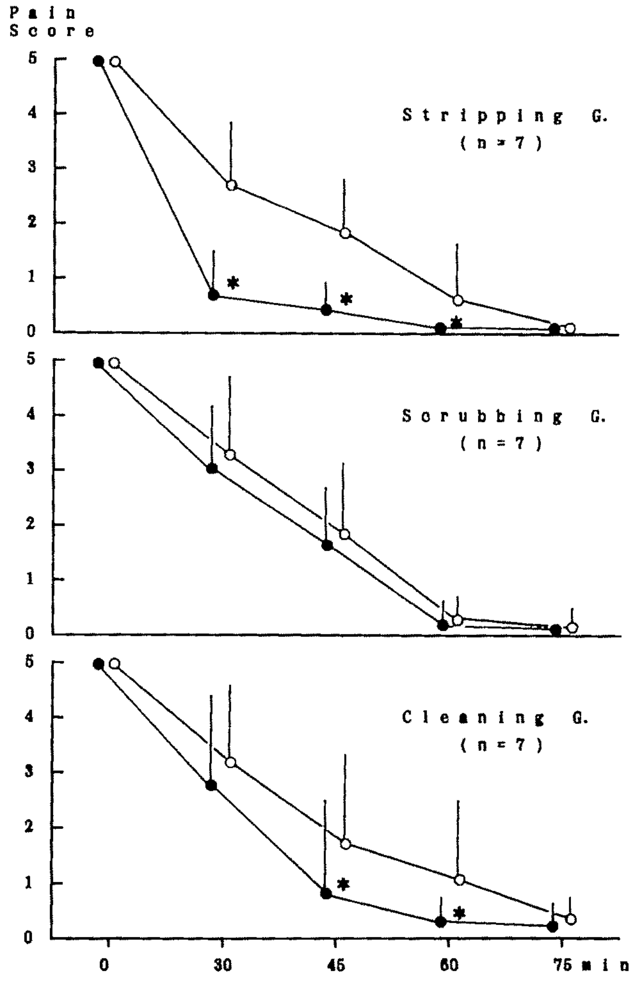

Figure 1. Comparison of pain scores between pretreated (*solid circles*) and unpretreated (*open circles*) sides after initiation of dermal patch anesthesia. G, study group. *Significantly lower compared with unpretreated side ($P < 0.05$).

the corresponding scores on the unpretreated side; however, these differences were not significant. In the cleaning study group, the 45- and 60-min pain scores on the pretreated side were significantly lower than the corresponding scores on the unpretreated side ($P < 0.05$).

Discussion

It is generally accepted that the absorption of drugs through the skin involves passive diffusion and that the main factor modulating transdermal absorption speed is penetration of the stratum corneum. Areas such as the palm and sole where the epidermal layer, especially the stratum corneum, is thick are unfavorable candidates for the transdermal absorption of drugs. On the other hand, diseased or injured skin is more permeable to transdermally applied drugs. Juhlin et al. (4) reported that after application of EMLA on the diseased skin of patients with psoriasis or atopic dermatitis, the plasma concentrations of lidocaine and prilocaine increased more rapidly and reached higher levels than were found for normal skin. Malkinson (5) reported that the skin-stripping procedure, which peels off the outer layer of the stratum corneum and reduces the barrier effect, was effective for transdermal absorption of hydrocortisone cream.

Among the pretreatments delivered in the present study, skin stripping was most effective for shortening the application time of 3% GA MHPh 2Na–10% lidocaine gel. Skin cleaning with benzine was aimed at removal of the sebum, a thin lipid layer covering the external surface of the stratum corneum, because 3% GA MHPh 2Na–10% lidocaine gel is hydrophilic. Contrary to our expectation, benzine pretreatment failed to accelerate the onset of skin analgesia in the dermal patch of 3% GA MHPh 2Na–10% lidocaine gel. Skin scrubbing with Skin-Pure jelly, which was expected to remove both the surface lipid and outer corneum layers of the epidermis, significantly shortened the application time of the lidocaine gel, as did skin stripping, although scrubbing was less effective than stripping.

In conclusion, skin pretreatments with stripping and cleaning shortened the onset of dermal patch anesthesia with 3% GA MHPh 2Na–10% lidocaine gel by approximately 30 and 15 min, respectively.

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Vomiting After Alfentanil Anesthesia: Effect of Dosing Method

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This double-blind study correlated the association of nausea and vomiting after alfentanil with its method of administration (bolus dose vs continuous infusion). Of 40 women undergoing lower abdominal gynecologic or laparoscopic surgery, 20 received an intravenous alfentanil (30 μg/kg) bolus dose for induction of anesthesia, with subsequent bolus doses of 10 μg/kg every 10 min, and 20 received the same induction dose delivered over 1 min, followed by an intravenous infusion at 1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$. The infusion group experienced more frequent nausea and vomiting than the bolus dose group (50% vs 30%, respectively; $P = 0.0001$). Laparoscopic surgery affected the incidence of nausea and vomiting independently of the method of alfentanil administration (75% for laparoscopic vs 17% for incisional procedures; $P = 0.0001$). Laparoscopy and alfentanil infusion combined synergistically to worsen the incidence of nausea and vomiting. We conclude that alfentanil infusion for laparoscopic surgery entails a high risk for nausea and vomiting.

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Administration of alfentanil by continuous infusion, as opposed to intermittent bolus doses, permits more rapid awakening and less frequent use of naloxone (1); however, as with other opioids, nausea and vomiting may delay hospital discharge. We hypothesized that the incidence of this annoying side effect might be related to the mode of administration. To test this hypothesis, we performed a double-blind, randomized study in a group of female patients known to be at high risk for postoperative nausea and vomiting (2,3).

Methods

With the approval of our institution's Committee for Human Studies, 40 women, ASA physical status I or II undergoing laparoscopic or lower abdominal gynecologic surgery, gave written, informed consent for alternating assignment to a bolus (B) dose or infusion (I) group. No patient received premedication. Usual monitoring was used. Each patient received glycopyrrolate (0.2 mg IV), followed by vecuronium (10 μg/kg IV) before induction of anesthesia. In group B (n = 20), alfentanil (30 μg/kg) was administered as a rapid intravenous push. In group I, alfentanil (30 μg/kg) was administered as two consecutive 30 s infusions of 15 μg/kg. In each group, methohexital (1 mg/kg) was administered after the alfentanil. Vecuronium (90 μg/kg), tracheal intubation, and 65%–75% inspired N_2O followed. Ventilation was controlled to maintain end-tidal CO_2 at 28–32 mm Hg.

Patients in group B received an alfentanil (10 μg/kg IV) bolus dose every 10 min for the balance of the procedure, whereas patients in group I immediately received an alfentanil infusion at 1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$. In group I, alfentanil was discontinued 5 min before the anticipated end of the procedure, whereas in group B, no further bolus doses were administered in the last 10 min of the procedure. A peripheral nerve stimulator guided additional administration of vecuronium. An 18F gastric tube was placed orally to evacuate air and gastric contents after intubation and before emergence from anesthesia. At the conclusion of surgery, glycopyrrolate (0.4–0.6 mg) and neostigmine (2.5–3.0 mg) reversed the neuromuscular blockade. Tracheal extubation occurred once the patients were fully awake.

Recovery room nurses who did not know the method of alfentanil administration collected the following data: the number of times the patient complained of nausea or vomited and the frequency of administration of antiemetics (prochlorperazine or benzquinamide), which were given to any patient who vomited more than once or who complained of nausea after vomiting once. A "prolonged postanes-

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Table 1. Incidence of Nausea With Vomiting After Alfentanil Anesthesia in 40 Women Undergoing Laparoscopic or Abdominal Gynecologic Surgery

Study group	Bolus dose	Infusion	Total
Laparoscopy	60% (6/10)	100% (6/6)	75% (12/16)
Incisional	0% (0/10)	29% (4/14)	17% (4/24)
Total	30% (6/20)	50% (10/20)	40% (16/40)

Results are presented as percent (number/total) of patients; $P < 0.0001$ laparoscopy vs incisional; $P < 0.0001$ bolus vs infusion; $P < 0.0001$ synergistic effect of infusion with laparoscopy.

Table 2. Incidence of Prolonged Postanesthesia Care Unit Stay[a] After Alfentanil Anesthesia in 40 Women

Study group	Bolus dose	Infusion	Total
Laparoscopy	10% (1/10)	50% (3/6)	25% (4/16)[b]
Incisional	0% (0/10)	0% (0/14)	0% (0/24)[b]
Total	5% (1/20)	15% (3/20)	10% (4/40)

Results are presented as percent (number/total) of patients.

[a] Prolonged stay occurred when total stay exceeded 120 min and discharge was delayed because of nausea or vomiting.

[b] $P = 0.0199$ laparoscopy vs incisional by Fisher's exact test.

thesia care unit stay" designation required delay of discharge because of nausea or vomiting and total stay >120 min.

Two-tailed unpaired Student's *t*-test compared demographic data between groups. To account for the confounding effect of surgical procedure on the incidence of nausea and vomiting, multinomial logistic regression was used to analyze the separate contributions of group and type of surgery and their interaction on the incidences of nausea and vomiting, antiemetic use, and prolonged recovery room stay (4); $P < 0.05$ denoted statistical significance.

Results

Patient groups did not differ with respect to demographic variables (age 35 ± 8 [SD] yr, weight 70 ± 14 kg). Laparoscopy accounted for 16 of the 40 procedures; the remaining 24 featured either lower abdominal or vaginal incision. As per experimental design, groups did not differ with respect to total alfentanil administered (1.15 vs 1.13 $\mu g \cdot kg^{-1} \cdot min^{-1}$ median doses). Groups also did not differ with respect to duration of anesthesia (121 ± 58 [SD] min for group I; 97 ± 43 min for group B; $P = 0.145$). However, a comparison of the total amount of alfentanil administered per kilogram body weight was indeterminant (median dose 128 μg/kg for group I vs 100 μg/kg for group B; $P = 0.055$).

Table 1 displays the incidence of nausea and vomiting according to type of surgery (laparoscopic or incisional) and group (bolus dose or infusion). Nausea and vomiting occurred with no specific temporal pattern. Some patients vomited before leaving the operating room, others several hours later. Multinomial logistic regression identified strong effects of both group and type of surgery on the incidence of nausea and vomiting: patients in the infusion group suffered a higher incidence of nausea and vomiting, as did laparoscopy patients. Infusion of alfentanil during laparoscopy combined synergistically to worsen the incidence of nausea and vomiting. Despite these significant effects, type of surgery and method of alfentanil administration did not affect the need for antiemetics. However, type of surgery did impact on the incidence of prolonged recovery room stay (Table 2). All four of the patients with prolonged stay underwent laparoscopy; three of these four received alfentanil by infusion.

Discussion

These data confirm previous studies showing an increased incidence of nausea and vomiting after laparoscopy (5,6). Causative factors may include insufflation of gas into the peritoneal cavity as well as residual effects from manipulation of the abdominal viscera (2). Nitrous oxide may cause vomiting by expanding air-filled cavities in the gastrointestinal tract and inner ear (7,8). Placement of an orogastric tube does not ensure complete evacuation of intragastric air. Does nitrous oxide exacerbate nausea and vomiting after laparoscopy? The data are conflicting. In one study (9), patients received isoflurane and nitrous oxide, enflurane and nitrous oxide, or isoflurane alone for anesthesia with respective incidences of emesis of 54%, 48%, and 52%. Yet, Felts et al. (10) found a significantly higher incidence of nausea and vomiting in patients receiving enflurane with nitrous oxide and oxygen, compared with patients receiving enflurane with air and oxygen (29.3% vs 9.3%, respectively). It is interesting to compare those emesis incidences with results in the current study of 40% overall and 75% for laparoscopy patients.

Other intravenous drugs, including methohexital and neostigmine (11), could have caused vomiting independent of the use of alfentanil. Because patients of many different surgeons participated in this study, differences in surgical technique could have contributed to the findings. These technical factors include the amount of intraperitoneal manipulation, the amount of gas used to insufflate the abdomen, dwell time of the gas, and the use of electrocautery.

This study utilized nausea with vomiting as the outcome event, rejecting nausea alone because of its insignificant impact on postanesthesia care unit stay. Vomiting without nausea that did not result from opioid administration was likewise not recorded. The current protocol also ignored any relationship between incidence of emesis and menstrual cycle timing (12).

Previous work (1) failed to show a difference in antiemetic requirement after alfentanil administered as a bolus dose versus infusion; however, that study comprised only 10 patients per group receiving a much higher dose of alfentanil (150 μg/kg). Furthermore, as the current data confirm, the use of an antiemetic does not always follow nausea and vomiting. Antiemetic choices include droperidol, prochlorperazine, benzquinamide, metoclopramide, and ephedrine (13). This protocol selected antiemetics based on their proven efficacy and minimal sedative effects.

Intermittent bolus injection results in a more variable plasma and, presumably, brain level of alfentanil. Perhaps the resulting sporadic egress of the opioid from the chemoreceptor trigger zone accounts for the lower incidence of nausea and vomiting found in group B. This intriguing possibility would require a much more sophisticated study than that undertaken here.

Could accumulation of alfentanil in patients receiving more total drug cause the increased incidence of nausea and vomiting? Although a larger study would be needed to answer this question, the authors believe that if accumulation occurs, it would exert far less effect than many other factors, such as type of surgery, choice of insufflation gas and dwell time for laparoscopies, use of electrocautery, and menstrual cycle timing.

All patients receiving alfentanil by infusion for laparoscopy suffered nausea and vomiting postoperatively, whereas no patient receiving bolus alfentanil for an incisional procedure experienced nausea or vomiting. Yet, the presence of a surgical incision increases the likelihood of postoperative discomfort and nausea (14). Opioid-induced dysphoria occurs more frequently when patients lack painful stimuli. Perhaps opioid-induced emesis behaves similarly. Opioid-induced emesis seldom occurs in the presence of opioid overdose.

Same-day discharge for laparoscopy patients mandates early ambulation. Opioids exert emetic effects in the area postrema, particularly the vestibular center. Active movement induces postoperative nausea and vomiting (15). Early ambulation before opioid effects have dissipated, even with the short-acting alfentanil, may foster motion disturbance-induced nausea and vomiting.

It is not surprising that groups did not differ in antiemetic use despite the difference in frequency of nausea and vomiting. Many patients experience nausea without vomiting or vomit once with relief of nausea. Although antiemetic prophylaxis might mitigate the effects on nausea and vomiting of alfentanil infusion during laparoscopy in women, these data do not address this issue.

Nausea with vomiting does prolong recovery room stay. One might infer from these data that nausea with vomiting is not a transient phenomenon, because it prolonged recovery room stay in a significant proportion of laparoscopy patients. We caution against this deduction, because only four patients experienced a prolonged stay.

Patients given alfentanil for outpatient laparoscopy without antiemetic prophylaxis experience a high incidence of postoperative nausea with vomiting, particularly when alfentanil is infused continuously. Although prolongation of recovery room stay may occur from administration of alfentanil by infusion for laparoscopy, confirmation requires a larger cohort. These data suggest avoidance of alfentanil infusions for outpatient laparoscopy in patients receiving methohexital and nitrous oxide.

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Ondansetron in the Treatment of Postoperative Vomiting: A Randomized, Double-Blind Comparison With Droperidol and Metoclopramide

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The prophylactic antiemetic efficacy of ondansetron was evaluated in a randomized, double-blind comparison with droperidol and metoclopramide in 66 patients undergoing general anesthesia for dilatation and curettage. Ten minutes before induction of anesthesia, 22 patients received a single intravenous dose of 8 mg of ondansetron, 22 others received 1.25 mg of droperidol, and the remaining 22 received 10 mg of metoclopramide. Anesthesia was induced with 3.3–5 mg/kg of intravenous thiopental and maintained with 65% nitrous oxide in oxygen and 2%–3% enflurane. Postoperatively, the incidence of vomiting was 13% with ondansetron, 45% with droperidol, and 54% with metoclopramide ($P < 0.05$; overall χ^2 test). There was no statistically significant difference in the incidence of nausea among the groups. Postoperative sedation and well-being scores were not significantly different among the groups. We conclude that preoperative prophylactic administration of ondansetron is superior to droperidol or metoclopramide in the prevention of emetic sequelae after general anesthesia for dilatation and curettage.

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Postoperative nausea and vomiting occur frequently in women undergoing general anesthesia for termination of pregnancy or therapeutic abortion (1); none of the currently used prophylactic antiemetic regimens are entirely successful (2). Metoclopramide has been thought to be an effective antiemetic by some investigators (3,4); others have considered its capacity to prevent postoperative emetic sequelae as questionable (5,6). There are also contradictory reports about the antiemetic efficacy of droperidol (3,5–7), and undesirable adverse effects have been described (8). Interest has therefore been focused on new antiemetic agents such as serotonin (5-HT) antagonists (2). Ondansetron is a selective 5-HT_3 receptor antagonist (9) that has proved to be effective in the prevention of cancer chemotherapy- and radiotherapy-induced emesis (10–12). Ondansetron has also appeared to be superior to metoclopramide in the control of cisplatin-induced emesis (13). Recently published investigations in patients undergoing general anesthesia showed its postoperative effectiveness when compared with placebo (14–16).

This study was designed to assess the efficacy and safety of ondansetron compared with metoclopramide and droperidol administered for prophylaxis of postoperative emesis in women undergoing general anesthesia for minor gynecologic surgery.

Methods

The study was reviewed and approved by our institution and conducted according to the principles of the Declaration of Helsinki. Sixty-seven ASA physical status I women, aged 15–37 yr, 7–14 wk pregnant, gave informed consent to participate in the study. They were scheduled to undergo general anesthesia for dilatation and curettage to terminate pregnancy or induce therapeutic abortion. Exclusion criteria included clinical or laboratory evidence of severe renal, hematologic, or hepatic abnormalities or history of drug abuse, previous allergic reactions to serotonin antagonists, or any antiemetic therapy within 24 h of surgery. The same standardized anesthetic technique was used in all patients. Subcutaneous midazolam (5 mg) was administered 45 min before induction of anesthesia. General anesthesia was induced with thiopental (3.3–5 mg/kg IV) and maintained in spontaneous ventilation with 2%–3% enflurane and 65% nitrous oxide in oxygen. The tracheas were not intubated, and stomachs were not suctioned. If required,

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intravenous alfentanil was used in doses up to 0.5 mg. During the operation, no patient received any antiemetic.

On the preoperative evening, all nulliparous patients were given 0.2 mg of prostaglandin gel vaginally. At the end of each operation, 0.2 mg of methylergometrine and 5 IU of oxytocin were intravenously administered. An infusion of 1000 mL of lactated Ringer's solution containing 10 IU of oxytocin was then started.

Ten min before induction of anesthesia, 22 patients received an intravenous injection of 8 mg of ondansetron; 22 received 1.25 mg of droperidol; and 22 received 10 mg of metoclopramide. Injections were performed in a double-blind fashion over 15 s, according to a randomized plan by an independent nurse who did not participate in any other activity of the study. Arterial blood pressure and heart rate were then measured noninvasively every minute for a 10-min period, and the patients were observed for any adverse effect of the injected antiemetic.

Postoperatively, after arrival in the recovery room, the patients were monitored for a 3-h period. At 30-min intervals, arterial blood pressure and heart rate were recorded by an independent recovery room nurse who did not know which antiemetic a patient had received. Nausea, retching, and vomiting were recorded as separate entities and were always assessed by the same recovery room nurse. If a patient vomited or spontaneously complained of nausea or retching, this was recorded. Every 30 min, each patient was asked if she was comfortable. If she replied affirmatively, she was not questioned again for 30 more minutes. If she did not feel comfortable, she was asked whether she felt sick or had pain. Responses to these questions were recorded. Pain treatment consisted of 500 mg of paracetamol in the form of a suppository. If patients requested an additional antiemetic, a suppository of 50 mg of mezlocine was administered. Totally effective antiemetic response was defined as no vomiting and no request for additional antiemetic. Sedation and well-being were graded on a three-point scale. The degree of sedation was assessed as 1 = asleep, 2 = drowsy, 3 = awake; well-being, after asking the patient, was graded as 1 = poor, 2 = moderate, and 3 = comfortable. Any other special observations were also recorded.

Cardiovascular and demographic data, sedation, and well-being scores as well as amount of anesthetics, duration of anesthesia, and time of awakening after anesthesia were analyzed with the Kruskall-Wallis test. The incidence of nausea and vomiting was compared with the χ^2 test followed by the Irwin-Snedecor test. A P value <0.05 was considered significant. All values are reported as mean ± SD.

Table 1. Demographic and Anesthetic Data of 66 Gynecologic Patients Receiving a Prophylactic Antiemetic Agent

	Ondansetron group (n = 22)	Droperidol group (n = 22)	Metoclopramide group (n = 22)
Age (yr)	26.5 ± 4.9	24.2 ± 7.2	24.9 ± 5.3
Weight (kg)	60.9 ± 10.3	57.6 ± 8.7	60.8 ± 10.0
Height (cm)	163 ± 7.1	160 ± 9.8	163 ± 6.2
Gestational age (wk)	9.5 ± 1.3	9.7 ± 1.5	9.2 ± 1.3
Duration of anesthesia (min)	14.7 ± 4.5	14.4 ± 4.8	13.8 ± 4.6
Time of awakening (min)	7.4 ± 2.1	7.7 ± 3.0	6.6 ± 3.9

Mean ± SD.

Results

A total of 67 patients entered the study. One patient had to be excluded, because she had a blood loss of 1500 mL intraoperatively and had received a total dose of 30 IU of oxytocin and 0.6 mg of methylergometrine to contract the uterus. Demographic data and gestational age in the three groups were not significantly different (Table 1). Analysis of preoperative questioning did not show any significant differences with regard to the incidence of allergies, alcohol or drug intake, or history of nausea and vomiting. Review of anesthesia protocols did not reveal significant differences in the amount of anesthetics, duration of anesthesia, or time of awakening after anesthesia (Table 1). One patient in the ondansetron group and one in the metoclopramide group received an additional 0.25 mg of alfentanil; one patient in the droperidol group received 0.5 mg of alfentanil. No significant change in mean arterial blood pressure or heart rate was associated with the antiemetic administration preoperatively or postoperatively (Figures 1 and 2).

In the postoperative observation period, ondansetron treatment resulted in a significantly lower ($P < 0.05$) incidence of vomiting compared with the two other groups: 3 of 22 (13%) patients in the ondansetron group, 12 of 22 (54%) patients in the metoclopramide group, and 10 of 22 (45%) patients in the droperidol group vomited. One patient in the ondansetron group, two patients in the dropridol group, and four patients in the metoclopramide group experienced more than one episode of vomiting. The occurrence of nausea, which was 40% in the ondansetron group, 63% in the metoclopramide group, and 50% in the droperidol group, however, was not statistically different. Thirteen of 22 (59%)

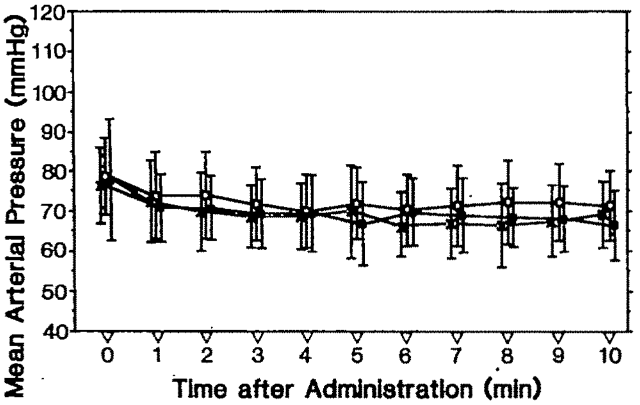

Figure 1. Mean arterial blood pressure before (0 = baseline value) and during the 10 min after injection of ondansetron (×), metoclopramide (■), and droperidol (O) before induction of anesthesia. All values are expressed as mean ± SD of 22 patients in each group. *Vertical lines* represent 1 SD.

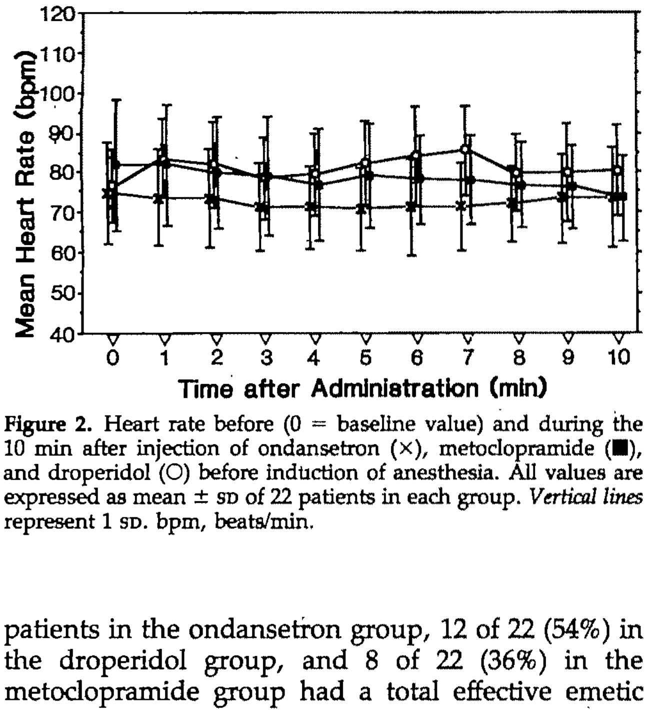

Figure 2. Heart rate before (0 = baseline value) and during the 10 min after injection of ondansetron (×), metoclopramide (■), and droperidol (O) before induction of anesthesia. All values are expressed as mean ± SD of 22 patients in each group. *Vertical lines* represent 1 SD. bpm, beats/min.

Table 2. Postanesthetic Sedation Scores of Subjects Receiving a Prophylactic Antiemetic Agent

	Time (min)					
	30	60	90	120	150	180
Ondansetron (*n* = 22)						
Mean	2.4	2.6	2.9	2.8	2.9	3.0
±SD	0.7	0.6	0.3	0.4	0.2	0
Droperidol (*n* = 22)						
Mean	1.9	2.5	2.7	2.9	3.0	3.0
±SD	0.6	0.6	0.3	0.3	0.2	0.2
Metoclopramide (*n* = 22)						
Mean	2.5	2.8	2.9	3.0	3.0	2.9
±SD	0.6	0.4	0.3	0	0	0.2

Sedation scores: 1 = asleep; 2 = drowsy; 3 = awake.

patients in the ondansetron group, 12 of 22 (54%) in the droperidol group, and 8 of 22 (36%) in the metoclopramide group had a total effective emetic response (statistically not different). An additional antiemetic was required by one patient subsequent to ondansetron, by three patients subsequent to metoclopramide, and by two patients subsequent to droperidol. There were no cases of protracted nausea or vomiting that needed further antiemetic therapy after the observation period.

Sedation (Table 2) and well-being scores were similar in all three groups. Apart from a short flush phenomenon and urticaria at the site of the injection in one patient immediately after administration of ondansetron, no other adverse effects were observed in this group. Subsequent to metoclopramide, one patient fell asleep, and, postoperatively, two patients experienced restlessness and shivering. After droperidol administration, three patients fell asleep, and, postoperatively, one patient complained of dizziness and five patients experienced restlessness and shivering.

Discussion

The incidence of postoperative nausea and vomiting is very high in women undergoing general anesthesia for dilatation and curettage (1,3,4). We therefore chose this patient population to evaluate the prophylactic antiemetic efficacy and safety of ondansetron compared with metoclopramide and droperidol, which are commonly used drugs. Ethical considerations dominated our decision not to use a placebo group, which is in agreement with Olver et al. (17). Although the mechanisms of postoperative emesis have not been fully elucidated, anesthesia plays a part in its etiology in addition to female gender, younger age, emotional response, and early stage of pregnancy (18–20). Thus, the use of enflurane (21) or nitrous oxide (22) may be associated with postoperative emetic sequelae. Furthermore, prostaglandins and methylergometrine are potential stimuli of nausea and vomiting (23,24). Narcotics may cause emetic symptoms, too (18); however, as the dose of the analgetic that we used was very small, only a limited statement with respect to antiemetic efficacy and opiates is possible.

In our trial of 66 patients, the incidence of postoperative vomiting was significantly less after prophylactic ondansetron (13%) compared with prophylactic metoclopramide (54%) and prophylactic droperidol (45%). This higher antiemetic efficacy of ondansetron may possibly be explained by the pharmacologic properties it is already known to have. Ondansetron as a highly selective 5-HT_3 receptor antagonist (9) blocks both peripheral and central 5-HT_3 receptors in a combined mode of action. Marty et al. (13) demonstrated the superiority of ondansetron to metoclopramide in reducing cisplatin-induced emesis in patients. Because an 8-mg intravenous dose of ondansetron administered before induction for general anesthesia with endotracheal intubation proved to be an effective antiemetic dose compared with placebo (25–27), we decided to use this amount of ondansetron for our study, too. Furthermore, Larijani et al. (15) and Bodner and White (16) showed that 8 mg of intravenous ondansetron administered during recovery from general anesthesia with intubation significantly lowered emetic episodes; Leeser and Lip (14) demonstrated that two 16-mg doses of oral ondansetron, one for premedication and one postoperatively, were effective in reducing postoperative emetic sequelae. For the prevention of postoperative nausea and vomiting, 10 mg of intravenous metoclopramide (3,5,28–30) or 1.25 mg of intravenous droperidol (5,8,29,30) has often been used, but there are contradictory findings in reports concerning the effectiveness of these two drugs. During recovery from mask anesthesia for minor gynecologic surgery, Madej and Simpson (3) reported that metoclopramide significantly reduced the incidence of nausea and vomiting, whereas Waldmann et al. (28) failed to prove that metoclopramide was effective when used in a similar anesthetic technique for therapeutic abortion. Cohen et al. (5) found that neither metoclopramide nor droperidol was capable of significantly lowering emetic symptoms after general anesthesia without tracheal intubation for therapeutic abortion. According to Melnick et al. (8), no significant differences in the incidence of postoperative nausea and vomiting were observed when droperidol was compared with placebo administered before induction of mask anesthesia for minor gynecologic surgery. On the other hand, antiemetic prophylaxis with droperidol after general anesthesia with endotracheal intubation was reported to be effective, whereas metoclopramide appeared to be ineffective (29,30). Our results show that the incidence of emesis but not of nausea was significantly lower in the ondansetron group compared with the other two groups. These findings are in agreement with Dundee and McMillan (31,32) who state that ondansetron was much more effective in preventing vomiting than in reducing nausea.

Lessin et al. (33) stated that two intravenous doses of 8 mg of ondansetron administered after the start of surgery and 8 h later did not prolong recovery time from general anesthesia compared with placebo. Kovac et al. (34) reported no significant difference, neither in recovery time nor in scores on a 10-point sedation scale, subsequent to 1, 4, or 8 mg of ondansetron administered 5 min before anesthesia compared with placebo. Using a three-point scale in our study, postoperative sedation and well-being scores were similar in the three groups. To assess postoperative sedation, Bodner and White (16) used a linear visual analogue scale with a range of 100 and described a significant difference between the ondansetron group treated with 8 mg preoperatively and the more sedated placebo group at 60 min after treatment, when 86% of the placebo group had received 20 mg of metoclopramide and 25 mg of hydroxyzine as rescue antiemetic. Furthermore, Madej and Simpson (3) did not observe significant differences with respect to postoperative sedation comparing preoperative use of 10 mg of metoclopramide with 2.5 mg of droperidol, whereas Cohen et al. (5) described a significantly longer recovery time from general anesthesia after 1.25 mg of preoperative droperidol compared with 10 mg of metoclopramide.

No adverse effects were observed in the ondansetron group in our study. This is in agreement with most authors, who describe only minor side effects in their investigations or judged them to be either unrelated or not likely to be due to ondansetron medication (14–16,25). In the literature, adverse reactions involving the nervous system after even small doses of metoclopramide have been described (3,35), and Scheller and Sears (36) report a case in which preoperative administration of the drug induced toxic neurologic reactions that were only apparent postoperatively. The use of low-dose droperidol has been described to be associated with extrapyramidal side reactions (3,37), and Melnick et al. (8) reported an incidence of postoperative anxiety or restlessness in 23% of patients, which may be related to the use of 1.25 mg of droperidol.

We conclude that 8 mg of intravenous ondansetron appears to be superior to 10 mg of metoclopramide or 1.25 mg of droperidol in preventing postoperative vomiting after general anesthesia for minor gynecologic surgery. Devoid of distressing side effects, ondansetron is a promising agent that may have an important influence on the control of perioperative emesis. Further studies comparing ondansetron with other antiemetic agents under conditions of general anesthesia for major surgical procedures and investigations to determine the optimal dose schedule for ondansetron are necessary to define its concrete position among the agents that are now commonly used.

We thank the anesthesia and recovery room nurses for their assistance.

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Comparative Effects of Ketorolac, Dezocine, and Fentanyl as Adjuvants During Outpatient Anesthesia

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The comparative effects of ketorolac, dezocine, and fentanyl were evaluated in 136 healthy female patients undergoing outpatient laparoscopic procedures according to a randomized, double-blind protocol. Patients received ketorolac (60 mg) or dezocine (6 mg) or fentanyl (100 μg, control group) before the start of the operation. A standardized general anesthetic technique consisting of midazolam (2 mg), fentanyl (50 μg), and propofol (2 mg/kg) for induction of anesthesia followed by propofol (120 $\mu g \cdot kg^{-1} \cdot min^{-1}$), vecuronium (1–2 mg), and 67% nitrous oxide in oxygen for maintenance of anesthesia, was used. In the postanesthesia care unit, 61% of patients in the fentanyl group received analgesic drugs for persistent pain, compared with 34% and 25% in the ketorolac and dezocine groups, respectively. Similarly, less postoperative fentanyl (mean ± SD) was required in the ketorolac (22 ± 33 μg) and dezocine (18 ± 35 μg) groups, compared with the fentanyl (58 ± 71 μg) group. However, 52% of the patients receiving dezocine required antinausea therapy in the postanesthesia care unit, compared with 20% and 18% in the fentanyl and ketorolac groups, respectively. Finally, recovery times were significantly shorter in the ketorolac (vs dezocine) group. Although both ketorolac and dezocine were effective alternatives to fentanyl when administered during outpatient laparoscopy, dezocine was associated with an increased incidence of postoperative nausea and a delayed discharge time compared with ketorolac.

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Potent, rapid-acting opioid analgesics (e.g., fentanyl) are widely used adjuvants during outpatient anesthesia (1). In addition to improving intraoperative conditions, these compounds provide effective pain relief on emergence from general anesthesia. Unfortunately, opioids can increase the incidence of postoperative nausea and vomiting in the outpatient setting (2). These adverse effects have stimulated the search for alternative drugs to provide analgesia during and after outpatient anesthesia.

Ketorolac (Toradol) and dezocine (Dalgan) are parenteral analgesics that have recently been approved for clinical use in the United States. Ketorolac, a nonsteroidal antiinflammatory drug that inhibits prostaglandin synthesis, is alleged to have comparable analgesic efficacy to morphine when administered for postoperative pain relief (3,4). Dezocine is a partial μ-receptor agonist that is slightly more potent than morphine when used for postoperative pain relief (5,6). Although dezocine produces opioid-related side effects, it is considered safer than pure opioid agonists because of its "ceiling effect" with respect to respiratory depression (6,7).

Given the limited data available on the perioperative use of ketorolac and dezocine (8–10), we designed a randomized, double-blind study to compare these two compounds with fentanyl, the most widely used intraoperative analgesic, when administered during ambulatory surgery. The intraoperative conditions, recovery times, and postoperative side-effect profiles were evaluated when these three analgesic compounds were administered as part of a standardized outpatient anesthetic technique.

Methods

We studied 136 healthy (ASA physical status I or II) women scheduled for elective laparoscopic procedures, according to a double-blind protocol approved by the Washington University Human Studies Committee. Written, informed consent was obtained from each patient in the preoperative holding area. Pa-

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tients were randomly assigned to receive a standardized "analgesic" dose of fentanyl (control group) or ketorolac or dezocine as an adjuvant during propofol-nitrous oxide anesthesia. The study medication (fentanyl [100 μg], ketorolac [60 mg], or dezocine [6 mg]) was prepared in a 2-mL numbered (unlabeled) syringe and was administered in a standardized manner: 1 mL IV, 1–2 min before induction with propofol and 1 mL IM after tracheal intubation. The surgeon, anesthesiologist, research nurse, and patient were all unaware of the type of analgesic medication. Pregnant women, women who had long-term analgesic or psychotropic drug therapy, and women with a history of opioid abuse or sensitivity to opioid-related side effects were excluded. Also excluded were patients with clinically significant cardiovascular, pulmonary, renal, hepatic, and neurologic diseases.

All subjects fasted for a minimum of 3 h before their scheduled surgery. No preanesthetic medication was administered. After placement of an intravenous catheter in the preoperative holding area, patients were asked to complete a baseline series of 100-mm visual analogue scales (VAS) (11–13) to assess sedation (0 = completely awake to 100 = extremely sleepy), anxiety (0 = calm to 100 = extremely nervous), pain (0 = no pain to 100 = severe pain), and nausea (0 = no nausea to 100 = severe nausea).

On arrival in the operating room, routine monitoring devices were applied, including an electrocardiogram, a noninvasive automatic blood pressure cuff, a pulse oximeter, and a precordial stethoscope. Patients were given midazolam (2 mg IV), to provide sedation, anxiolysis, and amnesia (14); lidocaine (50 mg IV), to minimize pain on injection of propofol (15,16); and fentanyl (50 μg IV), to minimize the hemodynamic response to laryngoscopy and tracheal intubation. Anesthesia was induced with propofol (2 mg/kg), at a rate of 1 $mg \cdot kg^{-1} \cdot min^{-1}$, with a Bard InfusOR pump (C.B. Bard, Inc., North Reading, Mass.). When the patient became unresponsive (loss of eyelid reflex), succinylcholine (1 mg/kg IV) was administered to facilitate tracheal intubation. A supplemental bolus dose of propofol (0.3 mg/kg) was administered if the patient manifested signs of inadequate anesthesia (e.g., hypertension, tachycardia, lacrimation). For maintenance of anesthesia, propofol was infused at an initial rate of 0.12 $mg \cdot kg^{-1} \cdot min^{-1}$ with 67% nitrous oxide in oxygen.

Before skin incision, vecuronium (1–2 mg IV) was administered to provide adequate surgical relaxation. Mean arterial blood pressure (MAP), heart rate (HR), respiratory rate, and hemoglobin oxygen saturation were recorded at 3–5-min intervals. Supplemental bolus doses of fentanyl (50 μg IV) were administered if increases in HR or MAP, or both, exceeded 20% of the preinduction baseline values and did not respond to a bolus dose of propofol (0.3 mg/kg IV) and an increase in the propofol infusion rate to 0.16 $mg \cdot kg^{-1} \cdot min^{-1}$. At the end of surgery, the propofol infusion was discontinued, and residual neuromuscular blockade was reversed with neostigmine (2.5–3 mg) and glycopyrrolate (0.4–0.6 mg IV). After reversal of residual neuromuscular blockade, nitrous oxide was discontinued.

Anesthesia time was recorded as the time from the start of induction to discontinuation of nitrous oxide. Operating time was determined from surgical incision to skin closure. Emergence times were evaluated at 30–60-s intervals from discontinuation of nitrous oxide until (a) the patient spontaneously opened her eyes (time to eye opening); and (b) the patient responded to a simple verbal command to squeeze the investigator's hand (time to following commands). Other recovery endpoints included the times from discontinuation of nitrous oxide until (a) the patient could sit up in a chair (time to sitting in a chair); (b) the patient tolerated fluids (time to oral intake); (c) the patient could walk unassisted (time to ambulation); and (d) the patient was judged to be fit for discharge or "home ready" (time to discharge).

The presence of pain and nausea were assessed at 30-min intervals after arrival in the postanesthesia care unit (PACU) by a research nurse who was unaware of the experimental treatment. Symptoms persisting on two successive evaluations were treated according to a standardized protocol. The requirements for analgesic (e.g., fentanyl) and antiemetic (e.g., metoclopramide) medications in the PACU were recorded. Discharge criteria to determine home readiness included orientation to time and place; stable vital signs on sitting up; and standing, ability to void, and ambulate without assistance (17). On entering the PACU and at 30-, 60-, 90-, and 120-min intervals postoperatively, the analogue scales were repeated to assess the patients' levels of sedation, anxiety, pain, and nausea. Finally, a follow-up questionnaire and telephone interview were completed 24 h after the operation to assess postdischarge side effects and patient satisfaction.

Data are reported as mean values ± SD (in the tables) or SEM (in the figures). Perioperative MAP and HR values for the three treatment groups were compared as a function of time after induction of anesthesia with repeated measures of analysis of variance. A Bonferroni correction was made for multiple comparison. In addition, analysis of variance and Student's *t*-test were used to analyze differences in the other continuous variables among the three treatment groups. Descriptive variables were analyzed with χ^2 tests, with P values <0.05 considered statistically significant.

Table 1. Demographic and Intraoperative Data for the Three Treatment Groups

	Fentanyl (n = 44)	Ketorolac (n = 44)	Dezocine (n = 48)
Age (yr)	33 ± 8	33 ± 8	34 ± 9
Weight (kg)	69 ± 17	65 ± 14	66 ± 13
ASA physical status (I/II)	32/12	34/10	39/9
Propofol dosages (mg)	470 ± 227	456 ± 201	441 ± 170
Supplemental fentanyl (μg)	20 ± 27	26 ± 40	25 ± 35
Operating time (min)	53 ± 38	55 ± 31	56 ± 29
Anesthesia time (min)	61 ± 38	62 ± 31	65 ± 24

Mean values ± SD (or number).

Results

The three analgesic treatment groups were comparable with respect to age, weight, ASA physical status, duration of laparoscopic procedure, and duration of anesthesia (Table 1). The propofol doses required for loss of consciousness (i.e., failure to respond to verbal commands) in the fentanyl, ketorolac, and dezocine groups were 79 ± 22, 83 ± 25, and 85 ± 27 mg, respectively. The number of patients requiring a supplemental bolus dose of propofol during the induction period was also similar in the fentanyl, ketorolac, and dezocine groups (5, 3, and 3, respectively). There were no significant differences in the total (or maintenance) dosage of propofol among the three groups. In addition, the supplemental fentanyl requirement during the operation was similar among the three groups (Table 1).

Changes in the hemodynamic variables during induction and maintenance of propofol-nitrous oxide anesthesia are summarized in Figure 1. After induction of anesthesia, there were comparable changes in MAP and HR among the three treatment groups. Immediately after laryngoscopy and intubation, the MAP returned to the preoperative baseline values in all three groups (Figure 1). The only significant hemodynamic difference among the three groups was a higher MAP at the end of anesthesia in dezocine-treated patients, compared with the fentanyl group ($P < 0.05$).

Times to eye opening and following verbal commands were similar in all three treatment groups (Table 2). Although not significantly different among the three groups, 51% of patients in the fentanyl group were able to move themselves from the operating table onto the stretcher, compared with 37% and 42% in the ketorolac and dezocine groups, respectively. The time to sitting up in a chair was also similar in all three treatment groups; however, the times to oral intake, ambulation, and discharge were significantly longer in the dezocine-treated patients compared with the ketorolac group. No significant differences were found between the ketorolac and fentanyl groups with respect to the recovery times (Table 2).

There were also no significant differences among the three groups with regard to preoperative sedation, anxiety, pain, and nausea VAS scores (Figure 2). The highest sedation VAS scores were recorded on arrival in the PACU and did not differ significantly among the three groups during the first hour in the PACU. However, ketorolac-treated patients reported a significantly lower sedation VAS score compared with the fentanyl and dezocine groups at 60 min after arriving in the PACU (Figure 2A). At the time of discharge from the PACU, all three groups still had significantly elevated sedation VAS scores compared with their preoperative baseline values ($P < 0.05$). No significant differences in anxiety VAS scores were found among the three treatment groups at any of the study intervals (Figure 2B). Patients receiving ketorolac had consistently lower pain VAS scores than those receiving fentanyl (Figure 2C). Furthermore, pain VAS scores in the ketorolac group had returned to their baseline values at the time of discharge. With the exception of patients in the dezocine group having higher nausea VAS scores at the 120-min interval than those receiving fentanyl, there were no significant differences in nausea VAS scores among the three groups (Figure 2D). However, 52% of the dezocine patients required antiemetic therapy in the PACU (vs 20% and 18% in the fentanyl and ketorolac groups, respectively). Furthermore, nausea VAS scores in the ketorolac group had returned to the preoperative baseline value at the time of discharge ($P < 0.05$).

Postoperative side effects and the requirements for parenteral analgesics and antiemetics are summarized in Table 3. A significantly higher percent of patients in the fentanyl group complained of pain in the PACU (73%) compared with patients in the ketorolac (43%) or dezocine (40%) groups. In the PACU, less analgesic (fentanyl) medication was required in the ketorolac (22 ± 33 μg, n = 34%) and dezocine (18 ± 35 μg, n = 25%) groups than in the fentanyl group (58 ± 71 μg, n = 61%). Additionally, the incidences of postoperative nausea and vomiting were significantly higher in the dezocine group than in the fentanyl and ketorolac groups ($P < 0.05$). The 24-h postoperative patient assessment questionnaire revealed that all three analgesic drugs were equally acceptable to the patients.

Discussion

Potent, rapid, and short-acting opioid analgesics are commonly used during ambulatory surgery because they improve surgical conditions (e.g., decrease pa-

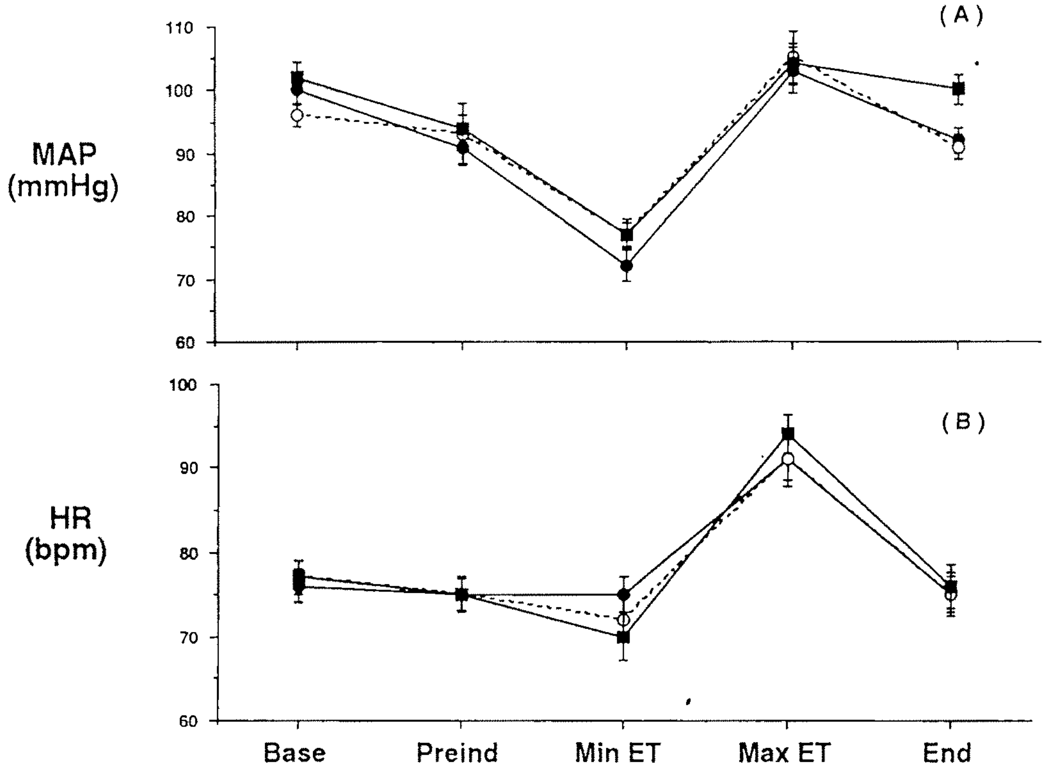

Figure 1. (A) Changes in mean arterial blood pressure (MAP) and (B) heart rate (HR) from initial baseline (Base), preinduction (Preind), minimal value during induction (Min ET), maximal value after intubation (Max ET), and at end of anesthesia (End) in fentanyl (*solid circle*), ketorolac (*open circle*), and dezocine (*square*) groups. Mean values ± SEM; **P* value <0.05 considered statistically significantly different from fentanyl (control) group. bpm, beats per minute.

Table 2. Recovery Times for Three Treatment Groups

	Fentanyl	Ketorolac	Dezocine
Time to eye opening (min)	3.7 ± 2.3	3.5 ± 1.9	4.2 ± 1.9
Time to following command (min)	4.4 ± 2.4	4.6 ± 2.5	5.2 ± 2.5
Time to sitting in chair (min)	75 ± 30	69 ± 22	78 ± 30
Time to oral intake (min)	96 ± 44	77 ± 31*	90 ± 44
Time to ambulation (min)	145 ± 58	122 ± 39*	165 ± 70
Time to discharge (min)	175 ± 75	141 ± 41*	194 ± 79

Mean values ± SD.
**P* < 0.05, significantly different from the dezocine group.

tient movement), and their anesthetic-sparing effects provide for a more rapid emergence from anesthesia (1,18). Although studies in the anesthesia literature suggest that dezocine also possesses anesthetic-sparing actions (19), no such data exist for ketorolac. Our study would suggest that ketorolac (60 mg) is similar to fentanyl (100 μg) and dezocine (6 mg) during outpatient laparoscopy. In addition, the intraoperative requirements for supplemental fentanyl were also similar in all three treatment groups.

The hemodynamic changes in response to tracheal intubation and surgical stimulation were identical in the three analgesic groups. Despite fentanyl (50 μg IV) and the analgesic study medication, MAP and HR values increased significantly after tracheal intubation in all three treatment groups. As all patients received similar amounts of propofol, it was not surprising that the awakening times were equally rapid (3.5 ± 1.9 to 4.2 ± 1.9 min). However, ketorolac-treated patients were able to tolerate oral fluids and ambulate sooner than patients in the dezocine group. More important, ketorolac-treated patients also required less time to be judged fit for discharge.

In the outpatient setting, intractable nausea, retching, and vomiting are among the leading causes of unexpected hospital admissions (20). Even transient nausea and vomiting can prolong the times to discharge after short gynecologic procedures (21,22). Thus, the longer time to discharge for the dezocine group was probably related to the higher incidence of emetic sequelae in that study group. Not surprisingly, the requirement for antiemetic therapy was also higher in the dezocine group. Our data for dezocine are consistent with previously published studies involving the adjunctive use of the agonist-antagonists nalbuphine and butorphanol during outpatient anesthesia (23,24). Even though >50% of the dezocine-treated patients received antiemetic therapy

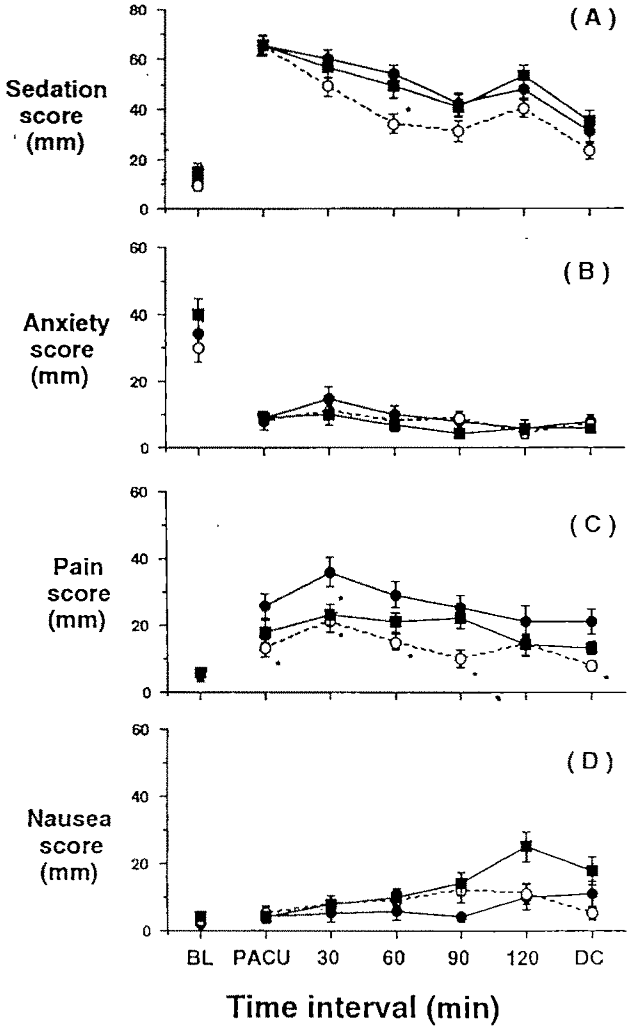

Figure 2. Visual analogue scores (VAS) in the three treatment groups: fentanyl (*solid circle*); ketorolac (*open circle*); dezocine (*square*). (A) Sedation VAS (0 = completely awake to 100 = extremely sleepy); (B) anxiety VAS (0 = calm to 100 = extremely nervous); (C) pain VAS (0 = no pain to 100 = severe pain); and (D) nausea VAS (0 = no nausea to 100 = severe nausea). Evaluation intervals included preoperative baseline (BL), on arrival in PACU (PACU), and at subsequent 30-min intervals until discharge (DC). Mean values ± SEM; *P values <0.05 considered statistically significantly different from fentanyl (control) group.

Table 3. Incidence of Pain and Other Side Effects Reported by the Nurse Observer on Direct Questioning, and Treatment for Three Treatment Groups in the Postanesthesia Care Unit

	Fentanyl	Ketorolac	Dezocine
Pain (%)	73	43[a]	40[a]
Nausea (%)	34	20	60[a]
Vomiting (%)	7	11	27[a]
Analgesic (%)	61	34[a]	25[a]
Antiemetic (%)	20	18	52[a]

[a] $P < 0.05$, significantly different from the control (fentanyl) group.

in the PACU, the nausea VAS score was still significantly higher than in the other two treatment groups 2 h after the operation.

In analyzing patient complaints of postoperative pain, both ketorolac and dezocine appeared to offer an advantage over fentanyl. The residual analgesia in the ketorolac and dezocine groups contributed to a decrease in the postoperative analgesic requirement. Compared with the fentanyl group, the patient pain and sedation VAS scores were consistently lower in the ketorolac group during the early postoperative period.

Given the improved postoperative analgesia associated with the use of ketorolac (vs fentanyl), it would seem to offer some clinical advantages over the popular rapid, short-acting opioid analgesic for outpatient laparoscopic procedures when administered during the intraoperative period. Additional studies are needed to evaluate the effectiveness of ketorolac when administered during other ambulatory surgery procedures involving both men and women.

The doses of the three analgesic compounds were chosen on the basis of open dose-ranging studies involving a similar patient population. In a preliminary study involving ketorolac (30–60 mg IM), we found that only the higher dose produced a significant anesthetic- and opioid-sparing effect (25). The dosages of the three analgesic study drugs were associated with similar intraoperative hemodynamic effects and comparable anesthetic and supplemental analgesic requirements; however, it is possible that a smaller dose of dezocine would have produced comparable postoperative analgesia with less nausea and vomiting. In addition, higher doses of fentanyl might have produced more effective postoperative analgesia without increasing side effects.

In conclusion, ketorolac (60 mg) appears to compare favorably with fentanyl (100 μg) when administered during outpatient laparoscopic procedures. In contrast to ketorolac, the use of dezocine (6 mg) resulted in an increased incidence of postoperative nausea and vomiting, contributing to a prolongation of the discharge time.

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Comparison of Desflurane With Propofol in Outpatients Undergoing Peripheral Orthopedic Surgery

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This study was undertaken to compare desflurane with propofol anesthesia in outpatients undergoing peripheral orthopedic surgery. Data were combined from two institutions participating in a multicenter study. Ninety-one patients, ASA physical status I or II, were each randomly assigned to one of four groups. After administration of fentanyl (2 μg/kg) and *d*-tubocurarine (3 mg), intravenous propofol was administered to induce anesthesia in groups I and II and desflurane in groups III and IV. Maintenance was provided by desflurane/N_2O in groups I and III, propofol/N_2O in group II, and desflurane/O_2 in group IV. Emergence and recovery variables, psychometric test results, and side effects were recorded by observers unaware of the experimental treatment. Patients in group II experienced less nausea than other groups ($P = 0.002$) despite this group having required more intraoperative fentanyl supplementation than groups III and IV ($P = 0.01$). Time to emergence, discharge, and psychometric test results were similar in all groups. Desflurane appears to be comparable with propofol as an outpatient anesthetic, facilitating rapid recovery and discharge home.

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The physiologic properties of desflurane suggest that it should be an effective anesthetic for use in outpatient surgery. The low arterial blood gas (0.42) and tissue gas partition coefficients predict a rapid increase and decrease of anesthetic partial pressure, facilitating both induction of and recovery from anesthesia (1,2). Minimal metabolism occurs in animals (3,4) and humans (5,6). The minimum alveolar anesthetic concentration (MAC) is 7.25% for subjects aged 18–30 yr and 6% for subjects aged 31–65 yr (7).

This randomized, prospective study was designed to evaluate the efficacy, side effects, and recovery profile of desflurane compared with propofol in outpatients undergoing peripheral orthopedic surgery. It was performed at two geographically separate institutions as part of a Food and Drug Administration (FDA) phase III testing of the clinical safety and efficacy of desflurane: University of Washington Medical Center (Center A) and University of Pennsylvania (Center B).

Methods

After approval by the human studies committees of both institutions, informed consent was obtained from 91 patients undergoing elective peripheral orthopedic surgery. The patients were ASA physical status I and II, male and female, ranging in age from 18 to 59 yr. Patients with a history of respiratory or cardiovascular disease, anemia, obesity, or chronic exposure to sedative-hypnotic, narcotic, or antidepressant medications were excluded from the study. A negative pregnancy test was required of participating women with childbearing potential.

Induction of Anesthesia

Patients at each center were randomly assigned to one of four anesthetic induction and maintenance groups (Table 1). Fentanyl (2 μg/kg) and *d*-tubocurarine (3 mg) were administered intravenously before induction of anesthesia. Anesthesia was induced with propofol (2.5 mg/kg IV) in groups I and II. An inhaled induction of anesthesia was performed in groups III (desflurane in 60% N_2O) and IV (desflurane in O_2). The concentration of desflurane delivered was initially set at 3% and thereafter increased by 3% every 4–6 breaths up to a maximum of 12%.

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Table 1. Induction/Maintenance Agents in the Four Study Groups

	Group I ($n = 22$)	Group II ($n = 23$)	Group III ($n = 24$)	Group IV ($n = 22$)
Induction	Prop	Prop	Des/N_2O	Des/O_2
Maintenance	Des/N_2O	Prop/N_2O	Des/N_2O	Des/O_2

Prop, propofol; Des, desflurane.

Anesthesia was maintained by desflurane in 60% N_2O in groups I and III and by desflurane in O_2 in group IV. Group II patients received propofol (100–200 $\mu g \cdot kg^{-1} \cdot h^{-1}$), with 60% N_2O for maintenance of anesthesia.

Patients were monitored in the usual manner. A modified Datex 250 Airway Gas Analyzer (Puritan-Bennett) was used to measure end-tidal CO_2, N_2O, O_2, and desflurane. Propofol was infused by a Baxter AS206H pump. Patients receiving desflurane were anesthetized with a modified Ohmeda DM5000 (Madison, Wis.) anesthesia machine. This machine was equipped with a temperature-controlled vaporizer (23°–25°C) pressurized to approximately 1520 mm Hg to allow delivery of desflurane, which has a boiling point of 23.5°C at atmospheric pressure.

All patients were paralyzed with succinylcholine (1.5 mg/kg IV) to facilitate tracheal intubation. Ventilation was controlled to maintain end-tidal CO_2 at 38 ± 3 mm Hg (mean ± SD). Anesthetic depth was adjusted to patient need by altering the concentration of inhaled desflurane up to a maximum of 12% end-tidal concentration in groups I, III, and IV or by varying the propofol infusion rate to a maximum of 200 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in group II. If the patient moved or experienced an increase in heart rate or mean arterial blood pressure >20% above awake measurements despite maximal protocol desflurane or propofol, up to three intravenous fentanyl bolus doses of 1 $\mu g/kg$ were administered per episode of light anesthesia. Muscle relaxation was provided by vecuronium (0.05–1 mg/kg), as clinically indicated (inadequate relaxation to perform surgery with no signs of inadequate anesthesia). Anesthesia was terminated on dressing placement. Arterial blood pressure and heart rate were recorded at 2-min intervals from the beginning of surgery until surgical incision, at 1-min intervals for the first 5 min of surgery, then every 15 min thereafter until dressing placement. End-tidal gas concentrations (CO_2, N_2O, desflurane), temperature, O_2 saturation, and propofol infusion rates were recorded at the same intervals as hemodynamics.

Emergence and Recovery

Variables recorded at emergence (measured in time from cessation of anesthesia) included time to opening eyes, finger squeeze, and telling name and date of birth.

Baseline psychometric testing utilizing p-deletion (8) and digit substitution tests (9) were performed in triplicate preoperatively to reduce practice effects. The best of the last two replications was used as the baseline against which subsequent performance was compared for each test. The p-deletion test consists of a sheet of 58 lines containing closely packed, single-spaced, random letters. Subjects are asked to cross out as many "p's" as they can in a 3-min period. The test provides a measure of alertness. The digit substitution test, a subtest of the Wechsler Adult Intelligence Scale (WAIS), consists of a single page with a symbol-number key at the top. The subject inserts the corresponding symbol for as many numbers as possible in a 2-min period. This test assesses the subject's ability to sustain focused attention and directed psychomotor functioning.

Recovery was evaluated by psychometric testing, pain scores, nausea and vomiting (noting the incidence, number of episodes, and severity, as well as the need for antiemetic medications), time to tolerating fluids, the sitting position, and discharge readiness. Postoperatively, psychometric testing was performed at 30-min intervals for 2 h if patients were able, regardless of whether they had received analgesics or antiemetics postoperatively. Patients unable to perform psychometric testing at any epoch received a score of zero for that time interval. Pain was assessed during the same 30-min intervals for the first 2 h after termination of the anesthetic. Pain was evaluated by the patient with verbal and visual analogue scales of 0–10 (0 = none; 10 = worst pain imaginable). Immediately postoperatively, analgesia was provided by fentanyl (25 μg) bolus doses, usually with a 100-μg maximum. Then, if necessary, patients received a dose of an oral narcotic analgesic as prescribed by their surgeon (nonstandardized by protocol). A four-point scale was used to characterize emetic symptoms: 0 = none; 1 = mild, noticeable, but not requiring treatment; 2 = moderate, requiring medication; and 3 = severe, unbearable and not responding to medication. Evaluations of nausea and vomiting occurred before administration of narcotic medications and when patients spontaneously complained of symptoms.

Choice of antiemetic therapy varied between the two institutions. Antiemetic therapy at Center A consisted of metoclopramide (10 mg IV); droperidol (0.625 mg IV, repeated once after 30 min if initially ineffective), then trimethopenzamide hydrochloride (250 mg) per rectum, or transdermal scopolamine (0.4 mg) applied to the mastoid. Center B offered atropine (0.4 mg IV), then prochlorperazine (5 mg IV).

Table 2. Demographics of 91 Patients Undergoing Peripheral Orthopedic Surgery

	Group I ($n = 22$)	Group II ($n = 23$)	Group III ($n = 24$)	Group IV ($n = 22$)	P
Gender (% female)	26.3	47.8	50.0	22.7	0.22
Age (yr)	33.5 (11.8)	34.1 (10.5)	36.8 (11.3)	31.6 (9.8)	0.46
Weight (kg)	75.7 (13.6)	74.5 (19.0)	75.0 (15.5)	81.6 (17.0)	0.44
Duration of surgery (min)	43.4 (24.8)	53.9 (45.6)	56.8 (41.0)	54.0 (24.9)	0.62
Previous surgery (%)	90.9	78.3	79.2	72.9	0.49

Mean (SD); no statistically significant differences between groups.

Statistical Analysis

Continuously distributed variables are presented as mean values (mean [SD]). One-way analysis of variance was used to compare variables measured only once. Comparisons of treatment effects of variables measured repeatedly over the postoperative period were made by significance testing of the group time interaction terms of the two-factor repeated measures analysis of variance with time as the repeated factor. Adjustment for center effects was by multivariate regression. Multiple-range testing was done by the Student-Newman-Keuls test when the analysis of variance omnibus null hypothesis was rejected. Binary coded or categoric data are presented as percentiles of the sample in the treatment group, and group differences were tested by χ^2 analysis with correction for continuity. Multiple-range testing for contingency tables was done by the critical ratio test, with one degree of freedom (10).

A two-tailed critical significance level of 0.05 was used throughout. The P values presented are nominal, with no correction for type I error due to the multiplicity of significance testing (other than that implicit in the multiple-range testing). Statistical computations were performed with SAS software (VMS release 6.06 on VAX 8600) (11).

Results

Data from the Center A ($n = 51$) and Center B ($n = 40$) were obtained using a common study protocol. These data were then combined so that the larger number of patients would contribute power to the analysis.

Demography (age, height, weight, ASA class, and history of previous surgery) was similar for all four treatment groups (Table 2). There were no statistically significant differences detected among groups I–IV or between centers.

Despite premedication with fentanyl (2 μg/kg), inhaled induction with desflurane (groups III and IV) was accompanied by signs of airway irritation and excitatory phenomena. These included coughing (36% [group III], 42% [group IV]); breathholding (26% [group III], 45% [group IV]); laryngospasm (5% [group III], 29% [group IV]); secretions (18% [group III], 25% [group IV]); and movement (5% [group III], 45% [group IV]). Treatment with assisted ventilation and positive pressure was successful in treating excitatory behavior in all but one patient who required relaxant because of hypoxemia (O_2 saturation of arterial blood [SaO_2] 65%) accompanying laryngospasm. As might be anticipated from the second gas effect, nitrous oxide shortened the time to loss of lash reflex and unconsciousness by an average of 40 s. Despite placing most intravenous cannulas in an antecubital vein to minimize the pain, 14% and 9% of patients in groups I and II, respectively, noted pain during induction of anesthesia with propofol.

Intraoperative arterial blood pressure and heart rate were stable, and mean values did not differ significantly among groups. Figures 1 and 2 show representative hemodynamic values. Extremes (minimal and maximal) of arterial blood pressure and heart rate during induction, intubation, and maintenance in each treatment group were similar, with one exception—the mean value for maximal mean arterial blood pressure during induction was significantly higher in group III (desflurane/N_2O) than in group II (propofol/propofol) (108 vs 95 mm Hg in groups III and II, respectively; $P = 0.04$). One group IV patient (desflurane/O_2 induction and maintenance) required atropine (1 mg) for transient complete heart block (heart rate 30 beats/min). Heart rate decreased just after intubation during repeated knee examinations. Heart rate increased to 120 beats/min after atropine administration. There were no additional dysrhythmias.

Mean end-tidal desflurane concentration (time-weighted average) for values recorded from onset of induction to cessation of anesthesia approximated 1 MAC in all groups receiving desflurane (Table 3). Similarly, the mean rate of propofol infusion from immediate postintubation to dressing placement was 170 $\mu g \cdot kg^{-1} \cdot min^{-1}$. More patients in group II (propofol induction and maintenance) required supplemental fentanyl than patients in groups III and IV ($P = 0.01$). The speed of emergence (Table 4) and recovery

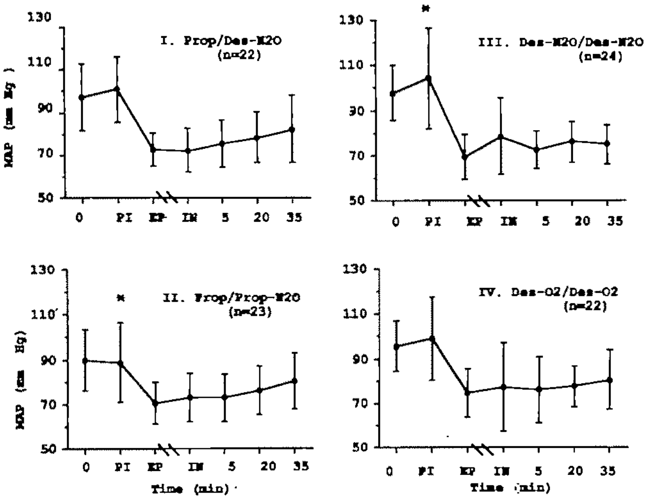

Figure 1. Representative mean arterial pressure (MAP) values (and standard deviations) showing values at 0, start of induction, immediately after intubation (PI), end of surgical preparation (EP), and surgical incision (IN), as well as at three 15-min increments during surgery for each treatment group. The *n* decreased after 35 min, secondary to surgical completion; therefore data are not presented. There was only one difference among groups as noted: *$P = 0.04$; group III > group II, immediately after intubation. Prop, propofol; Des, desflurane.

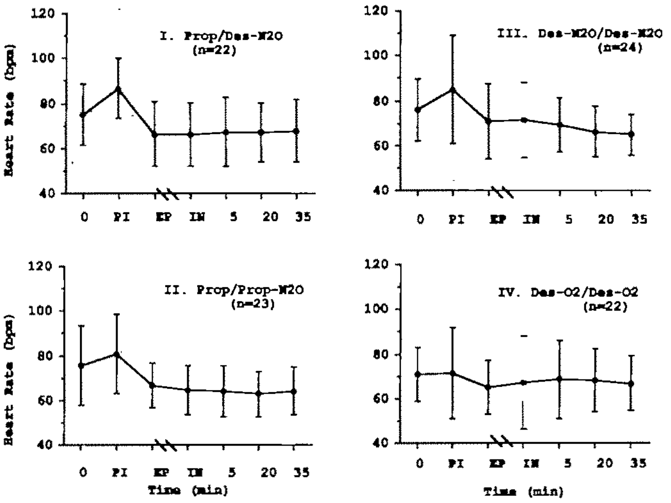

Figure 2. Representative mean heart rate (and standard deviations) from induction showing values at 0, start of induction, immediately after intubation (PI), end of surgical preparation (EP), and surgical incision (IN), as well as at three 15-min increments during surgery. The *n* decreased after 35 min, secondary to surgical completion; therefore these data are not presented. There were no detectable differences among groups. Prop, propofol; Des, desflurane; bpm, beats/min.

(Table 5) was similar in all four groups, with a few exceptions. Time to sitting was faster for patients undergoing propofol induction and maintenance (group II) compared with group IV patients ($P = 0.01$). Patients receiving propofol induction and maintenance (group II) tolerated fluids sooner ($P = 0.03$) than patients receiving a desflurane anesthetic without propofol (groups III and IV). Discharge readiness did not differ significantly among groups.

Psychometric test results were similar in all groups (Figure 3). Mean values had not returned to baseline by the time of discharge. The percent of patients attempting the tests at each time epoch are shown in Figure 4. As noted previously in Methods, those unable to attempt a test were assigned a zero score.

Nausea was experienced less often by patients who had propofol induction and maintenance compared with patients who received desflurane for maintenance (group II vs groups I, III, and IV; $P = 0.002$). Patients in group II had the least severe nausea compared with all other groups ($P = 0.003$). Group II patients also experienced fewer episodes of nausea, compared with groups III and IV ($P = 0.002$), and group I less than group III. Medical intervention for nausea or vomiting was also required more often by patients in groups I, III, and IV than in group II ($P = 0.02$).

Five patients required hospital admission: one in each of groups I and III for nausea and vomiting, one for pain in each of groups I and III, and one for urinary retention in group IV. All admitted patients were discharged in satisfactory condition the following morning. There were no other significant adverse effects identified in any patient.

Discussion

We thought it justifiable to combine data from the two institutions because of (a) use of a common protocol; (b) demographically similar groups; and (c) relatively minor differences in clinical practice between the two institutions. Analyses were done both on a center and pooled basis. Because of space limitations, we have presented only the combined, nonadjusted data. However, the results were very consistent at the two institutions, with no interactions between treatment and center effects and no differences in conclusions between centers except for emetic variables.

Induction of anesthesia proceeded as expected in all groups. Inhaled induction was rapid (142 s with N_2O, 188.4 s without) but was accompanied by significant excitatory phenomena in 20%–40% of patients. Previous investigators have reported similar excitatory phenomena during inhaled induction with desflurane (7,12–14). A smoother inhaled induction might have been attained by a more gradual increase of inspired desflurane concentration, by the addition of intravenous medications to obtund airway reflexes and irritability, or by the addition of CO_2 (15).

Pain on injection of propofol is commonplace (16,17) and is greater when infused into small distal

Table 3. Intraoperative Anesthetic Doses in the Four Study Groups

	Group I (n = 22)	Group II (n = 23)	Group III (n = 24)	Group IV (n = 22)
Induction	Prop	Prop	Des/N_2O	Des
Maintenance	Des/N_2O	Prop/N_2O	Des/N_2O	Des
Prop ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	—	170 (70)	—	—
Des (ET %)[a]	5.4 (1.4)	—	6.0 (1.3)	6.7 (1.3)
Patients requiring additional fentanyl (%)[b]	27.3	60.9[c]	0	9.1
Fentanyl (μg)	24.1 (41.8)	88.2 (146.9)[d]	0	24.5 (89.7)

Prop, propofol; Des, desflurane; ET, end-tidal.
Mean (SD).
[a] Time-weighted average.
[b] Fentanyl required after maximal protocol adjustment of maintenance agent.
[c] $P = 0.01$ by analysis of variance and Student-Neuman-Keuls test comparing group II with groups III and IV.
[d] $P = 0.01$, group II > groups I, III, and IV.

Table 4. Emergence From Anesthesia in the Four Study Groups

	Group I (n = 22)	Group II (n = 23)	Group III (n = 24)	Group IV (n = 22)	P
Induction	Prop	Prop	Des/N_2O	Des	
Maintenance	Des/N_2O	Prop/N_2O	Des/N_2O	Des	
Emergence (min from cessation of anesthesia)					
Open eyes	10.0 (4.6)	9.7 (6.5)	7.3 (3.6)	9.7 (6.3)	0.29
Squeeze fingers	11.0 (5.5)	10.6 (6.3)	7.8 (4.0)	10.1 (6.2)	0.19
Tell name	11.7 (5.9)	11.2 (6.3)	9.2 (4.0)	10.7 (6.7)	0.50
Tell date of birth	12.0 (6.2)	11.3 (6.7)	9.6 (3.9)	10.7 (6.8)	0.55

Prop, propofol; Des, desflurane.
Mean (SD).

Table 5. Recovery From Anesthesia in the Four Study Groups

	Group I (n = 22)	Group II (n = 23)	Group III (n = 24)	Group IV (n = 22)	P
Induction	Prop	Prop	Des/N_2O	Des	
Maintenance	Des/N_2O	Prop/N_2O	Des/N_2O	Des	
Recovery (min from cessation of anesthesia)					
PO fluids	54.7 (34.4)	43.4 (19.2)	79 (48.6)	81.8 (55.6)	0.03[a]
Sitting	87.4 (63.0)	40.7 (32.7)	79.9 (55.4)	96.0 (72.2)	0.01[b]
Nausea (%)	40.9	13.0	66.7	54.6	0.002[c]
Nausea score	0.68 (0.89)	0.17 (0.49)	1.0 (0.91)	0.91 (0.92)	0.003[d]
Nausea episodes	0.45 (0.60)	0.17 (0.49)	1.0 (0.88)	0.77 (0.92)	0.002[e]
Vomiting (%)	13.6	8.7	33.3	22.7	0.16
Nausea/vomiting requiring medical intervention (%)	36.4	4.3	41.7	40.9	0.02[c]
Ready for discharge (min after entering recovery room)	143 ± 41.3	129.6 ± 26.2	147.6 ± 62.5	160.8 ± 63.8	0.25

Prop, propofol; Des, desflurane; PO, oral.
Mean (SD).
[a] Group II < groups III and IV.
[b] Group II < group IV.
[c] Group II < groups I, III, and IV.
[d] Group I significantly different from groups II and III; group II significantly different from group III.
[e] Group II significantly different from groups III and IV; group I significantly different from group III.

veins (18). Despite the fact that we selected larger, more proximal veins for injection of propofol, we still observed pain on injection in a significant number of patients (14% and 9% in groups I and II, respectively). Possibly, the incidence could be reduced further by incorporation of lidocaine with propofol before injection (19).

Intraoperative hemodynamics were relatively stable and did not vary significantly between groups, with the exception that mean arterial pressure during

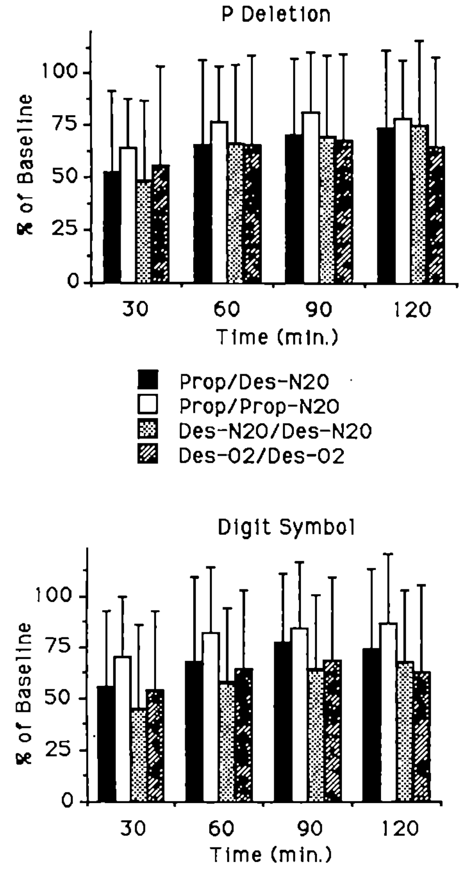

Figure 3. Percent of baseline performance on p-deletion and digit substitution tests. Groups did not differ in their performance. Prop, propofol; Des, desflurane.

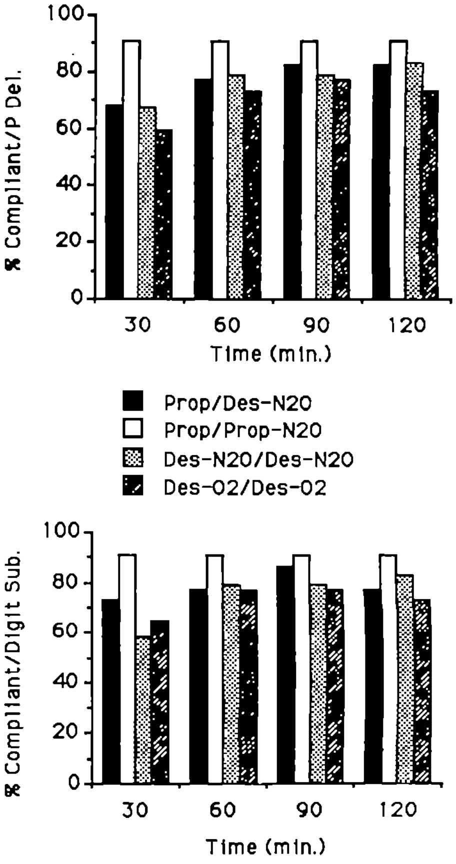

Figure 4. Percent of patients who attempted neuropsychometrics (% Compliant) at each time epoch. No statistical difference was detected among groups on either the p-deletion (P Del.) or the digit substitution (Digit Sub.) test. Prop, propofol; Des, desflurane.

induction was greater in group III than in group II (Figures 1 and 2). This transient elevation of mean arterial pressure was not judged to be clinically significant. The hemodynamic values recorded are consistent with those reported by other investigators who found that desflurane is similar to isoflurane in its hemodynamic effects (20).

Both anesthetics permitted rapid adjustment of anesthetic depth in response to surgical stimuli. The mean end-tidal desflurane concentrations were 5.4% in group I, 6.0% in group III, and 6.7% in group IV. The highest concentrations were attained in patients receiving desflurane in oxygen without nitrous oxide, as might be anticipated. End-tidal concentrations are somewhat in excess of what might be expected in groups I and III on the basis of observations of Rampil et al. (21) who reported a MAC of 4.0% (age 18–30 yr) and 2.8% (age 31–65 yr) for desflurane in surgical patients also receiving 60% N_2O. The concentrations that we report reflect adjustments made during surgery as clinically indicated in the judgment of the persons performing anesthesia, as opposed to the response to surgical incision. The use of hemodynamic variables as a means of evaluating depth may have contributed to maintaining a greater depth of anesthesia than was necessary for surgery. The use of the tourniquet in our patients may also have added to the anesthetic requirement.

It was noted that more patients receiving a propofol/N_2O anesthetic required fentanyl supplementation (Table 3) (i.e., owing to failure of maximal rate of propofol infusion to prevent movement or hemodynamic changes). This is in part related to the design of our protocol, which limited the rate of propofol infusion to 200 $\mu g \cdot kg^{-1} \cdot min^{-1}$. It may also reflect the fact that propofol is thought to be devoid of analgesic effects (22). Desflurane may provide an element of analgesia, as is the case with other halogenated anesthetics (23).

In contrast to Apfelbaum et al. (24) who reported a more rapid emergence with desflurane anesthesia compared with propofol anesthesia, we did not see a more rapid emergence in patients receiving desflurane. As an example, they recorded a time to emergence of 18 min after propofol anesthesia versus 10 min after desflurane/O_2 anesthesia (there was no desflurane/N_2O induction/maintenance group). Only emergence variables (early recovery, not later recovery variables) were noted in this study. There are several important aspects of the methodology of the two studies that might account for the differences in results. Their subjects were human volunteers who underwent 60 min of anesthesia designed to maintain hemodynamics within 20% of baseline without the use adjuvant of agents. Desflurane concentrations were not reported. In our study, the average duration of anesthesia was 43–57 min. Anesthesia was titrated to surgical stimulation as well as hemodynamic criteria. Surgical patients may require more anesthesia, which may influence speed of emergence. Fentanyl was administered preoperatively in our study and as necessary during anesthetic maintenance. Thus, the use of adjuvant medications, coupled with a desflurane concentration that may have been higher than that used in volunteers, may have contributed to longer emergence times, possibly obscuring differences between anesthetics. Normal volunteers may demonstrate less variability in response variables. This would increase power to detect a given difference as statistically significant. In any event, the differences in the speed of emergence observed by Apfelbaum et al. (24) were small and probably not of much clinical significance.

Psychometric testing also failed to demonstrate differences in the speed of recovery. This did not appear to be due to lack of sensitivity of the test, because baseline values of cognitive functioning (psychometric testing) were not achieved by any group by the time of discharge despite patients meeting the standard discharge criteria (25). It is of note in this regard that Fletcher et al. (26) recorded significant differences in the rate of return of psychomotor function when comparing patients anesthetized with desflurane versus isoflurane. However, they excluded all patients from their analysis who received analgesics or antiemetic medications during recovery from anesthesia. There are three commonly used strategies for those subjects who cannot perform neuropsychometric testing for any reason: (a) censor the noncompliant subjects; (2) assign zero scores to the noncompliant patients (as we chose to do, because bias is only present when subjects are able to do tests but refuse—this was not the case with our subjects); or, as Fletcher et al. (26) did, (c) assign the lowest score recorded for any subject in the sample at any point. Conceivably, these individuals might perform differently on psychometric testing. In our study, the decision was made in advance to evaluate all patients regardless of what additional antiemetic or analgesic drugs they received. Our study may therefore be more representative of the realities of clinical practice but less likely to demonstrate subtle differences among anesthetic techniques.

The choice of psychometric tests may also have affected the ability to detect differences among groups. The digit substitution and p-deletion tests appear to be less sensitive to changes or differences in cognitive function than choice-reaction or critical flicker fusion test, as noted by Hindmarch and Bhatti (27). It is acknowledged that the administration of antiemetics and analgesics may have affected subject performance.

The previously reported antiemetic effect of propofol (28–30) was reaffirmed in our study. Patients undergoing propofol induction and maintenance experienced significantly less nausea than patients receiving desflurane anesthetics. These patients were able to take fluids sooner despite receiving more intraoperative fentanyl. The shorter time to sitting may be attributable to the lower incidence of nausea in group II.

The use of preinduction doses of fentanyl (2 μg/kg) may have contributed to nausea. This drug was included in the protocol to blunt the hemodynamic response to endotracheal intubation. A variety of other factors may contribute to postoperative nausea. These include gender, age, perioperative narcotics, and duration of anesthesia (31). The four treatment groups in this study were of comparable gender, age, and surgical duration, and all received preoperative narcotics. Of interest, there was a slightly greater incidence of nausea reported by patients at Center A, although the relative trends among groups were similar, and statistically significant findings remained after adjusting for the effects of the two study centers in multivariate regression. The difference in the incidence of emetic symptoms between the two centers might be explained simply by random variation, by differences in the method of patient reporting, nursing practice, or intercenter difference in clinical practice. Patients at Center A were routinely offered postoperative oral fluids; at Center B, fluids were provided only on strong request. Although restriction of oral fluids per se has not been shown to decrease the incidence of nausea and vomiting (32), Watcha et al. (33) reported an inverse relationship between the "time to first oral intake" and the incidence of emesis.

In conclusion, our data suggest that desflurane is clinically comparable with propofol for outpatient orthopedic surgery insofar as safety and general efficacy are concerned. Speed of emergence, as measured by time to eye opening, following commands, and achieving orientation, did not differ among groups. Although there were some differences in achieving various milestones of recovery, time to taking fluids and ability to tolerate the sitting position were more rapid in patients undergoing a propofol anesthetic; however, fit for discharge times did not differ among groups. Both anesthetics provide for rapid emergence and acceptable recovery times.

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Use of Flumazenil for Intraoperative Arousal During Spine Fusion

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The intraoperative arousal test is used to detect potential damage to the spinal cord during spine fusion. We determined whether a continuous midazolam infusion, the effects of which are antagonized by flumazenil when the arousal test is needed, is associated with good control of the timing of arousal and with no adverse reactions. In a randomized study of 20 patients (10 in each group), we compared arousal with flumazenil during midazolam-narcotic anesthesia with an arousal test done during halothane-nitrous oxide anesthesia, both under conditions of controlled hypotension. Motor responses to verbal command were obtained 39.1 ± 36.0 s (mean ± SD) after the injection of flumazenil in eight patients. Two patients from this group awoke spontaneously 6 and 8 min after terminating the administration of nitrous oxide and midazolam but remained sedated up to the time of the test itself. In the halothane group, arousal occurred 26 ± 8.3 min after halothane administration was terminated and 10.1 ± 3.3 min after nitrous oxide was stopped. Two of the patients in this group moved, owing to early arousal 5 and 8 min before the scheduled time and needed reinstatement of anesthesia. In four patients in the halothane group, we had to wait 3–11 min after the scheduled time before satisfactory arousal was achieved. One of the patients in the halothane group showed a motor deficit of the lower limbs during the wake-up test that disappeared after decreasing the spine correction. There were no adverse reactions except for occasional shivering in the recovery period. No patient complained of any recall or unpleasant memories during the postoperative interview the following morning. We conclude that the midazolam-flumazenil technique for intraoperative arousal may be preferable to the discontinuation of halothane. The administration of flumazenil under these circumstances induces a rapid, easily controllable arousal, even under conditions of controlled hypotension.

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Early detection of potential damage to the spinal cord during spine fusion for correction of scoliosis is highly desirable, because a delayed diagnosis is often associated with permanent deficit (1). One of the techniques for spinal cord function monitoring is the intraoperative arousal test described by Vauzelle et al. (2). This approach gained popularity owing to its simplicity, safety, and reproducibility (1,3).

Accurate timing of the arousal test is crucial so that the patient will be awake at the right moment and any unnecessary delay in the surgical procedure will be prevented. A new anesthetic technique was described for the intraoperative arousal test (4). This method is based on a continuous midazolam infusion supplemented by narcotics, muscle relaxants, and controlled ventilation. When the arousal test was needed, the benzodiazepine antagonist flumazenil was used to antagonize the effect of midazolam with good control of the timing of arousal and no adverse reactions (4). However, this technique was not tested during the conditions of controlled hypotension, which is often used during spine surgery, nor was it compared with arousal from halothane-nitrous oxide anesthesia.

Methods

After obtaining approval by the Medical Ethics Committee, 20 ASA physical status I and II patients, aged 13–28 yr, who were scheduled for spinal fusion and instrumentation (Cotrel-Debousset procedure) for idiopathic scoliosis, were enrolled in the study after giving informed consent. Patients with psychologic problems, mental retardation, or neuromuscular deficit were excluded from the study.

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After oral administration of diazepam (0.1 mg/kg) 1 h preoperatively, anesthesia was induced with 3–4 mg/kg of thiopental, preceded by fentanyl (0.1 mg IV), midazolam (2–3 mg), and pancuronium (1 mg). Paralysis was obtained by administration of succinylcholine (1 mg/kg), and the trachea was intubated. Ventilation was maintained with a mixture of 30% oxygen and 70% nitrous oxide, with an end-tidal carbon dioxide concentration of 30–38 mm Hg. A single dose of 10 mg of *d*-tubocurarine with 3 mg of pancuronium was introduced for moderate muscle relaxation at the beginning of surgery. An arterial cannula for continuous blood pressure recording, central venous line, nasogastric tube, urinary catheter, and esophageal thermometer were placed in all patients. Nitroprusside (0.25% solution) was infused in all patients to maintain mean arterial blood pressure between 50 and 60 mm Hg. Lactated Ringer's solution was administered at the rate of 6 $mL \cdot kg^{-1} \cdot h^{-1}$, and blood was transfused if the blood loss was estimated to be >10% of the estimated blood volume.

Patients were randomly assigned to one of the two study groups. In the midazolam group (*n* = 10), anesthesia was maintained with a continuous midazolam infusion at a rate of 0.2–0.3 $mg \cdot kg^{-1} \cdot h^{-1}$, supplemented with 1–2 μg/kg of fentanyl every 30 min up to 30 min before the scheduled arousal test. Intraoperative arousal in the midazolam group was produced as follows: 10 min before the scheduled arousal test, midazolam infusion and nitrous oxide were stopped, and ventilation continued with 100% oxygen. Absence of neuromuscular blockade was confirmed with a nerve stimulator. A dose of 3 μg/kg of flumazenil was injected, after which spinal cord function was assessed by the response to verbal command to move both hands and then both feet.

In the halothane group (*n* = 10), anesthesia was maintained with 0.75% halothane and 1–2 μg/kg of fentanyl every 30 min up to 30 min before the intraoperative arousal test. Intraoperative arousal was produced by stopping the administration of halothane 20 min before the scheduled arousal. Ten minutes later, when absence of neuromuscular blockade was confirmed with a nerve stimulator, nitrous oxide was stopped and ventilation was continued with 100% oxygen. Spinal cord function was assessed as mentioned previously. In both groups, anesthesia was then resumed with thiopental (3 mg/kg IV), fentanyl (0.1 mg IV), pancuronium (0.06 mg/kg), nitrous oxide, and halothane.

At the end of surgery, neuromuscular blockade was reversed with intravenous neostigmine and atropine and the tracheas were extubated. The following morning, the patients were interviewed for any recall or unpleasant memories of the procedure.

Table 1. Clinical Data for 20 Patients Undergoing Spine Fusion

	Flumazenil group (*n* = 10)	Halothane group (*n* = 10)
Age (yr)	16.6 ± 4.9	16.1 ± 3.6
Weight (kg)	46.9 ± 6.8	50.0 ± 10.7
Gender (M/F)	10:0	5:5
Length of anesthesia up to arousal (min)	181.5 ± 43.8	187.5 ± 34.6
Total length of procedure (min)	239.0 ± 42.5	246.5 ± 34.6
Temperature at arousal (°C)	35.6 ± 0.8	35.7 ± 0.8
P_{ETCO_2} pressure at arousal (mm Hg)	31.4 ± 4.7	31.9 ± 5.2
Sa_{O_2} at arousal (%)	98.0 ± 1.0	98.0 ± 1.0
Estimated blood loss (mL)	1216 ± 742	1508 ± 704

M, male; F, female; P_{ETCO_2}, end-tidal partial pressure of CO_2; Sa_{O_2}, oxyhemoglobin saturation.
Mean ± SD.

Intergroup comparisons of patient data, length of surgical procedure, temperature, end-tidal partial pressure of CO_2, oxyhemoglobin saturation, estimated blood loss, and hemodynamic data were performed by unpaired Student's *t*-test. Intragroup analysis of hemodynamic changes before and after arousal was performed by a paired *t*-test. Differences were considered significant at $P < 0.05$. Results are presented as mean ± SD.

Results

No differences were observed between the two groups with respect to age, gender, weight, length of surgical procedure, temperature, end-tidal partial pressure of CO_2, oxyhemoglobin saturation, and estimated blood loss (Table 1). Motor response to verbal command was obtained 39 ± 36 s after the injection of flumazenil in the midazolam group. Two patients in this group awoke spontaneously 6 and 8 min after termination of nitrous oxide and midazolam administration but remained sedated and motionless up to the time of the test itself.

Arousal in the halothane group occurred 26 ± 8 min after the halothane was turned off and 10 ± 3 min after administration of nitrous oxide was terminated. Two of the patients in this group showed early signs of arousal 5 and 8 min before the scheduled time. They moved and needed a short reinstatement of anesthesia with halothane to allow the surgeon to complete the instrumentation before the test. In four other patients in this group, we had to wait 3–11 minutes after the scheduled time before satisfactory arousal was achieved.

Mean arterial blood pressure increased significantly during intraoperative arousal in both groups

Table 2. Mean Arterial Pressure (MAP) and Heart Rate (HR) During the Arousal Test in the Two Study Groups

	Flumazenil group (n = 10)	Halothane group (n = 10)
MAP (mm Hg)		
Baseline[a]	55.8 ± 5.4	56.7 ± 4.3
During arousal	71.0 ± 5.3[b]	66.7 ± 5.3[b]
After arousal[c]	56.5 ± 6.6	59.5 ± 5.6
HR (beats/min)		
Baseline[a]	82 ± 12	85 ± 16
During arousal	93 ± 13	87 ± 15
After arousal[c]	82 ± 14	85 ± 16

Mean ± SD.
[a] Twenty minutes before scheduled arousal.
[b] $P < 0.01$ compared with baseline MAP.
[c] Twenty minutes after arousal.

and returned to initial baseline values after reinstatement of anesthesia (Table 2). The changes in arterial blood pressure were similar in both groups. There was no significant change in mean heart rate between prearousal and postarousal values in either of the groups (Table 2). There were no anxiety reactions, violent movements, or any other untoward incidents during the tests. One of the patients in the halothane group demonstrated good voluntary control of the hands during the wake-up test but absence of leg movement. The spine correction was decreased to the point that the motor deficit disappeared, and the patient was able to move her feet again.

In the recovery room, no neurologic deficit could be noted in any of the patients, including the patient previously mentioned. Two patients in the flumazenil group and three in the halothane group had their ventilation controlled for a short period postoperatively owing to low systemic temperature. No adverse reactions, except for occasional shivering, were recorded during the recovery period. No patient complained of any recall or unpleasant memories during the postoperative interview the following morning.

Discussion

The need for early detection of potential damage to the spinal cord during spine fusion for correction of scoliosis is unquestionable (1). There is, however, disagreement in the literature with regard to the best method for doing so, the two commonly used techniques being the intraoperative arousal test (1,2) and neurophysiologic monitoring by somatosensory evoked potentials (5).

The intraoperative arousal method is easy to use and does not require the special training and equipment that are mandatory for the neurophysiologic surveillance technique. Another problem with the latter technique is the limited choice of anesthetics, some of which distort the signal and limit its usefulness (6). The exact timing of the arousal test, however, requires experience and astute clinical judgment on the part of the anesthesiologist. The timing of arousal is especially imprecise when the anesthetic method used is based on a narcotic-muscle relaxant technique combined with inhaled anesthetics.

The recent introduction of the specific benzodiazepine antagonist flumazenil (7) has made possible the use of the intraoperative arousal technique based on the midazolam-flumazenil anesthetic method (4). The results of our study demonstrate that the benzodiazepine-antagonist technique enables the anesthesiologist to time the wake-up test accurately, even when the surgeon is not able to precisely determine the time of the test in advance. The benzodiazepine-flumazenil technique enabled us to keep the patients sedated and ready to be aroused <1 min before the test was needed. Two patients in the halothane group woke up prematurely, moved, and required the reestablishment of anesthesia for a short time. For other patients in this group, we had to wait up to 11 min after the scheduled time before satisfactory arousal was achieved.

We used a moderate dose of 3 μg/kg of flumazenil, a dose that has not been associated with any reported side effects (8,9). Indeed, none of the patients showed any abnormal response to flumazenil except for transient increases in arterial blood pressure. Patients in the halothane group showed the same significant increase in arterial blood pressure during the arousal period. We thus assume that the increase in arterial blood pressure was due to the arousal itself, not the injection of flumazenil. This assumption is supported by previous work that demonstrated that cardiovascular responses to arousal with flumazenil are minimal, even in patients with severe cardiac disease (10). The observed cardiovascular responses were not different from those seen when patients are allowed to recover spontaneously (11). Additional studies demonstrated that benzodiazepine antagonism with flumazenil does not produce acute anxiety or evidence of stress response (12). Indeed, the increases in arterial blood pressure were moderate, and the highest arterial blood pressures after arousal were still in the acceptable range.

We conclude that the midazolam-flumazenil technique for intraoperative arousal may be preferable to the discontinuation of inhaled anesthetics. The administration of flumazenil under these circumstances induces a rapid, easily controllable arousal, even under conditions of controlled hypotension.

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Intraoperative Monitoring of Tibialis Anterior Muscle Motor Evoked Responses to Transcranial Electrical Stimulation During Partial Neuromuscular Blockade

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We studied the feasibility of recording motor evoked responses to transcranial electrical stimulation (tc^{e}-MERs) during partial neuromuscular blockade (NMB). In 11 patients, compound muscle action potentials were recorded from the tibialis anterior muscle in response to transcranial electrical stimulation during various levels of vecuronium-induced NMB. The level of NMB was assessed by accelerometry of the adductor pollicis muscle after train-of-four stimulation of the ulnar nerve. The compound muscle action potential was also recorded from the tibialis anterior muscle after direct stimulation of the peroneal nerve (M-response) as an alternative means of assessing the degree of NMB. In all patients, tc^{e}-MERs could be recorded reliably during anesthesia with N_2O and a continuous infusion of sufentanil (0.5 $\mu g \cdot kg^{-1} \cdot h^{-1}$). An intact train-of-four was present in all patients, and the amplitude of the first twitch was recorded and designated as the control value. Before administration of vecuronium, the M-response amplitude was 9.6 ± 3.6 (mean ± SD) mV, and the tc^{e}-MER amplitude was 1.21 ± 0.66 mV. Although administration of vecuronium (0.05 mg/kg) resulted in loss of the mechanical adductor pollicis response in 8 of the 11 patients, the M-response and the tc^{e}-MER remained recordable. Subsequently, during an infusion of vecuronium, adjusted to maintain one or two mechanical responses to train-of-four stimulation, the average M-response to peroneal nerve stimulation was 5.2 ± 2.5 mV (53% of the control value), and tc^{e}-MER amplitude was 0.59 ± 0.36 mV (59% of the control value). During incomplete relaxation, there was good correlation between the amplitude of the M-response and that of the tc^{e}-MER ($r = 0.75$; $P < 0.01$). The ratio of tc^{e}-MER amplitude to M-response amplitude remained constant, suggesting that it may be feasible to use the amplitude of the M-response to "calibrate" the tc^{e}-MER amplitude during vecuronium administration. The data indicate that tc^{e}-MER monitoring is feasible during clinically effective levels of NMB.

(Anesth Analg 1992;75:584–9)

Intraoperative recording of motor evoked responses to transcranial electrical or magnetic stimulation (tc^{e}-MERs) provides a method for monitoring conduction in descending motor pathways during operations in which there is a risk of spinal cord injury. The addition of tc^{e}-MERs to intraoperative somatosensory evoked response (SSER) monitoring may decrease the occurrence of false-negative results that have been reported during SSER monitoring (1,2); however, tc^{e}-MER monitoring imposes some restrictions on anesthetic technique. Our experience, and that of others, suggests that the anesthesiologist is limited to a predominantly intravenous technique, because compound muscle action potential (CMAP) responses to transcranial stimulation are abolished at very low concentrations of volatile anesthetics (3,4). In addition, it has been asserted that recording CMAPs in response to transcranial stimulation precludes administration of neuromuscular blocking drugs (5); however, various surgical procedures may be difficult to accomplish with anesthesia that omits both volatile anesthetics and muscle relaxants. Accordingly, this study was undertaken to determine whether tc^{e}-MERs could be elicited and interpreted in the presence of incomplete neuromuscular blockade.

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Methods

Patient Selection

The study was approved by the local Human Subjects Committee. Written, informed consent was obtained from 11 patients scheduled to undergo lumbar laminectomy/discectomy or lumbar spinal fusion. The patients were between 18 and 50 yr of age and were of ASA physical status I or II. Patients with objective bilateral sensory or motor deficits, treated or untreated epilepsy, current or recent use of medications known to lower seizure thresholds (e.g., tricyclic antidepressants and phenothiazines), cardiac disease, and diabetes were excluded. Unilateral sensory disturbances or unilateral subjective weakness did not result in exclusion, although recordings were made from the uninvolved extremity.

No premedication was administered. Some patients received sufentanil (5–10 μg IV) preoperatively. Anesthesia was induced with etomidate (0.3–0.5 mg/kg). Succinylcholine (1–1.5 mg/kg IV) was administered to facilitate tracheal intubation. After administration of sufentanil (1–1.5 μg/kg IV), anesthesia was maintained with 66% nitrous oxide in oxygen and a continuous infusion of sufentanil (0.5 $\mu g \cdot kg^{-1} \cdot h^{-1}$ IV). When signs of light anesthesia were observed (heart rate or mean arterial pressure increase by >15% of baseline), a supplemental 10-μg bolus dose of sufentanil was administered, and the infusion rate increased by 25%.

A commercially available accelerometer designed to quantify neuromuscular blockade during clinical anesthesia (Biometer Accelograph, Biometer International, Odense, Denmark) was used to titrate the administration of vecuronium. The device quantitates the mechanical adductor pollicis (thenar) response to train-of-four (TOF) ulnar nerve stimulation at 15-s intervals by measuring the acceleration of a transducer attached to the thumb. The accelerometry technique is based on the principle that acceleration is proportional to force when mass remains constant. Because no preload is required, it is easier to set up than conventional mechanomyography. The signal from the acceleration transducer is amplified, and the "height" of the first response (T1h) is displayed as a percent of height of the first response during calibration. During neuromuscular blockade, the TOF ratio (T4/T1 × 100) is displayed when four responses to TOF stimulation are present. When less than four responses are detected, only the actual number of responses (zero, one, two, or three) is displayed. Moderate or "surgical" neuromuscular blockade is considered to be present when only one mechanical response to TOF stimulation is recordable. This corresponds to depression of the first twitch to 5%–10% of control (6).

Twenty minutes after administration of succinylcholine, the accelerometer was applied and calibrated. The patient's hand was taped to a splint to ensure unimpeded movement of the thumb. A TOF constant-current square-wave stimuli (2 Hz) of 200-μs duration was applied to the ulnar nerve every 15 s through silver/silver chloride pediatric electrocardiographic electrodes. Light abrasion of the skin was performed before electrode application to ensure that stimulus electrode impedance was <2 kΩ. Stimulus current was 60 mA, which in all patients was at least twice the current that was found to be supramaximal.

A constant voltage stimulator, specifically designed for transcranial electrical stimulation (Digitimer D180A, Digitimer Ltd., Welwyn Garden City, U.K.) was used to stimulate the motor cortex. This stimulator delivers an electrical stimulus of up to 1200 V, with a user-selectable time constant of 50 or 100 μs. Stimulus intensity is set with a rotary dial that is calibrated as percent of maximal stimulator output. Stimulation was accomplished by way of conventional silver/silver chloride electroencephalographic disk electrodes attached to the scalp with collodion and filled with electrode jelly. The anode was placed at the vertex (C_z, International 10-20 System), and the cathode was placed 7 cm anteriorly. The 100-μs time constant was used in all subjects.

The threshold stimulus intensity needed to elicit a tc^e-MER in the anesthetized patient was determined, as was the stimulus intensity at which further increases in intensity did not elicit larger responses. A stimulus intensity 20% above that found to be supramaximal was used throughout the study (500–700 V). A Cadwell Quantum 84 evoked-response analyzer was used to record CMAPs from the tibialis anterior muscle by Grass gold cup electroencephalographic electrodes applied in belly/tendon fashion. Electrode impedance was maintained at <2 kΩ. The CMAP signal was filtered between 10 and 3000 Hz, and amplifier gain was adjusted as necessary to obtain maximal vertical resolution. A time base of 100 ms was used. For each measurement, three single-sweep tc^e-MERs were acquired at 15-s intervals. The average value of these responses was used for the statistical analysis.

The tibialis anterior CMAP response to supramaximal peroneal nerve stimulation was recorded as a means of assessing the degree of neuromuscular blockade at the site of tc^e-MER recording. This response is known in the neurophysiologic literature as the muscle (M) response. To elicit the M-response, Grass needle electrodes were inserted 3 cm apart perpendicular to the peroneal nerve at the fibular head. Constant-current (60 mA) square-wave pulses of 200-μs duration were used. The recording variables and electrodes were the same as those used for the tc^e-MER recording.

After recording of baseline tc^e-MERs and M-responses (after incision, at least 30 min after induction of anesthesia and full recovery from succinylcholine), a bolus dose of 0.05 mg/kg of vecuronium was administered. Five minutes after the bolus dose of vecuronium, recordings were repeated. When neuromuscular transmission had recovered to at least one mechanical thenar response to TOF stimulation, a continuous infusion of vecuronium was started at an initial rate of 0.05 mg·kg^{-1}·h^{-1} and adjusted to maintain one to two responses to TOF stimulation. The number of responses to TOF stimulation and the percent twitch height (T1h) at the time of acquisition of each tc^{e}-MER were recorded.

Data acquired at the following intraoperative intervals were compared: *interval A*—during surgical stimulation, but before administration of vecuronium (control interval); *interval B*—5 min after administration of the loading dose of vecuronium (at which time no response to TOF stimulation was present in most subjects); and *interval C*—during the infusion of vecuronium when one or two responses to TOF stimulation were present. To minimize the influence of possible fluctuations in anesthetic depth and varying levels of surgical stimulation, for each patient the average of two to six measurements recorded during vecuronium infusion was used rather than one single measurement. All data were used in the linear regression analysis.

The tc^{e}-MER and M-response waveforms were stored on magnetic disk and analyzed off-line. For the tc^{e}-MER, onset latency and maximal peak-to-peak amplitude were determined. For the M-response, the maximal peak-to-peak amplitude of the response was determined. For each pair of waveforms, the ratio between tc^{e}-MER and M-response amplitude was calculated. The accelerometer values (twitch height of the first response [T1h] as a percent of the control response and number of responses to TOF stimulation) were recorded at the time of recording tc^{e}-MER and M-response.

Data are expressed as mean ± SD. Paired *t*-tests corrected for multiple comparisons were used to compare the data acquired at intervals B and C with the control data (interval A). A linear regression analysis of M-response versus tc^{e}-MER amplitude data pairs was performed on the pooled data from all patients.

Results

During anesthesia with sufentanil/N$_2$O, before administration of vecuronium (interval A), reproducible baseline tc^{e}-MERs and M-responses could be recorded in all patients (Table 1). The tc^{e}-MER amplitude was 1.21 ± 0.66 (mean ± SD) mV. The M-response amplitude was 9.6 ± 3.6 mV. The average ratio of tc^{e}-MER amplitude to M-response amplitude before administration of vecuronium was 0.13 ± 0.06.

Table 1. Adductor Pollicus T1 Twitch Height (T1h), Tibialis Anterior Muscle Response to Peroneal Nerve Stimulation (M-Response), and the Transcranial Electrical Motor Evoked Response (tc^{e}-MER) at Various Levels of Neuromuscular Blockade in 11 Patients Undergoing Laminectomy/Discectomy or Lumbar Spinal Fusion

	Interval A (control) (*n* = 11)	Interval B (*n* = 8)	Interval C (*n* = 11)
No. of responses to TOF stimulation (adductor pollicis accelerometry)	4	0	1–2
T1 twitch height (% of control)	100	0	15.1 ± 7.4^a
tc^{e}-MER amplitude			
(mV)	1.21 ± 0.66	0.29 ± 0.23^a	0.59 ± 0.36^b
(% of control)	100	30.3 ± 18.6^a	59.5 ± 32.4^b
M-response amplitude			
(mV)	9.6 ± 3.6	2.5 ± 2.2^a	5.2 ± 2.5^a
(% of control)	100	21.8 ± 14.8^a	52.6 ± 13.9^a
tc^{e}-MER/M-response ratio	0.13 ± 0.06	0.15 ± 0.10	0.13 ± 0.06

Interval A, during anesthesia and surgery before administration of vecuronium; interval B, 5 min after administration of 0.05 mg/kg of vecuronium (T1h% = 0); interval C, during infusion of vecuronium to maintain one to two responses to train-of-four (TOF) stimulation.

Results are mean ± SD.

^{a}$P < 0.05$, compared with control.

^{b}$P < 0.05$, compared with control.

Five minutes after injection of the initial bolus dose of vecuronium (0.05 mg/kg) (interval B), complete suppression of the mechanical adductor pollicis twitch was observed in 8 of the 11 patients. Figure 1 shows M-response and tc^{e}-MER waveforms from one patient before administration of vecuronium (interval A), 5 min after administration of vecuronium (interval B—no mechanical thenar response), and during infusion of vecuronium when one response to TOF stimulation was present (interval C). Despite complete suppression of mechanical twitch in most patients, both the M-response and tc^{e}-MER were recordable in all subjects (Table 1) at all times after the bolus dose of vecuronium and during the subsequent infusion (average vecuronium infusion rate 1.1 ± 0.27 μg·kg^{-1}·min^{-1}).

During the infusion of vecuronium (interval C) when one or two responses to TOF stimulation were present, T1h was 15.1% ± 7.4%. The average amplitude of the M-response to peroneal nerve stimulation was 5.2 ± 2.5 mV, and tc^{e}-MER amplitude was 0.59 ± 0.36 mV (53% and 59% of control, respectively). Regression analysis of the pooled data from all patients revealed that there was a linear relationship between M-response and tc^{e}-MER amplitudes (Figure 2). The ratio of tc^{e}-MER to M-response amplitude was unaltered at any level of neuromuscular blockade

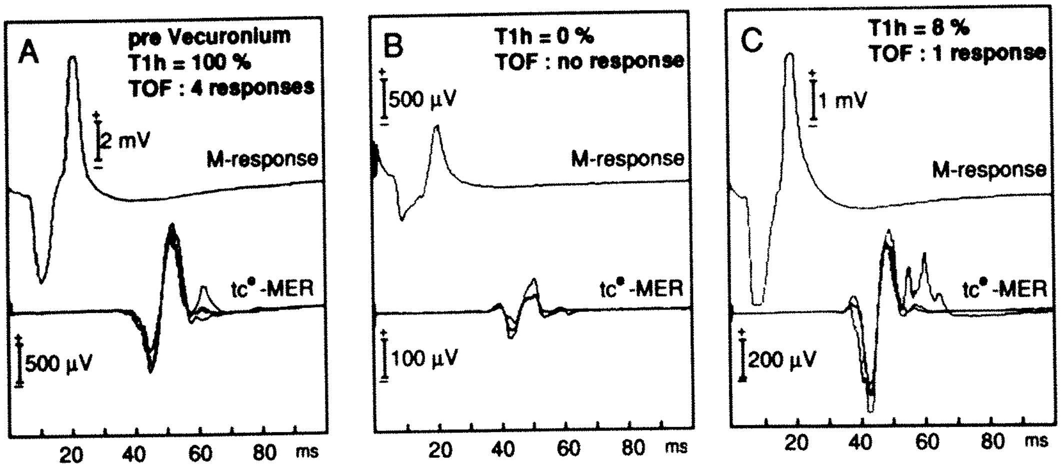

Figure 1. Tibialis anterior response to peroneal nerve stimulation (M-response) and transcranial electrical motor evoked response (tc^{e}-MER) from the same muscle before administration of vecuronium (**A**), 5 min after vecuronium (0.05 mg/kg) administration (**B**), and during a continuous infusion of vecuronium adjusted to maintain at least one response to TOF stimulation (**C**). T1h, twitch height of the adductor pollicis (as measured by accelerometry) after ulnar nerve stimulation, expressed as a percent of the control response measured during anesthesia before vecuronium administration; TOF, number of adductor pollicis responses detected after TOF stimulation.

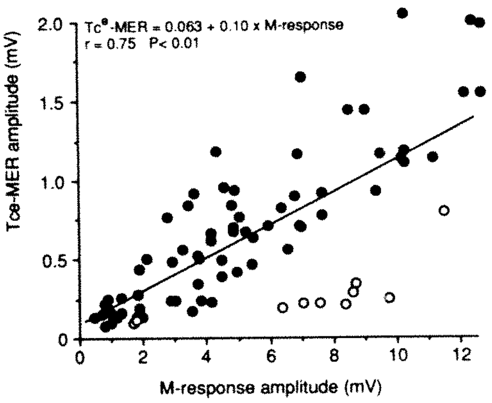

Figure 2. Relationship between tibialis anterior muscle M-response amplitude and tibialis anterior tc^{e}-MER amplitude at various levels of NMB with vecuronium (pooled data from 11 patients). The level of NMB is expressed as number of responses to TOF stimulation. The *open circles* represent data from the two patients who had a very low tc^{e}-MER/M-response amplitude ratio. Abbreviations as in Figure 1.

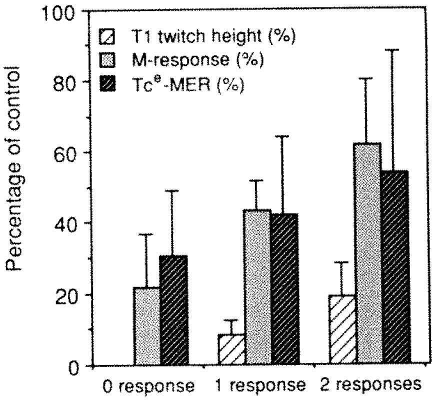

Figure 3. Relative depression of adductor pollicis T1 twitch height, tibialis anterior muscle M-response, and tc^{e}-MER during various levels of NMB, expressed as the number of twitch responses occurring after TOF stimulation of the ulnar nerve. Data are mean ± SD; $n = 6$ patients. Abbreviations as in Figure 1.

(NMB) (Table 1, Figure 3). In two patients (represented by the open circles in Figure 2), the ratio of tc^{e}-MER to M-response amplitude was obviously lower (0.025 and 0.034) than in the remainder of the group. Post-hoc examination revealed no explanation for these apparent "outliers." Preinduction tc^{e}-MERs were not recorded. Accordingly, we do not know whether these two patients, for either technical or biologic reasons, had small baseline responses or whether their tc^{e}-MERs were more depressed by the anesthetic technique than the group as a whole; however, a linear relationship between tc^{e}-MER and M-response changes was nonetheless apparent.

Average onset latency of the tc^{e}-MER before administration of vecuronium was 33.1 ± 2.57 ms. No changes in tc^{e}-MER latencies occurred at any level of neuromuscular blockade.

Discussion

The results of the present study demonstrate that tc^{e}-MERs can be readily recorded from the tibialis anterior muscle in the presence of partial neuromuscular blockade during anesthesia with sufentanil and nitrous oxide. Furthermore, they indicate that when clinical neuromuscular blockade, as judged by the TOF at the thenar eminence, has been achieved with vecuronium, the amplitude of the M-response of the tibialis anterior muscle may be reduced by as little as 55%–60% of preparalysis values. Accordingly, the results suggest that clinically substantial degrees of

NMB need not be viewed as incompatible with intraoperative tc^e-MER recording. In the clinical situation, it will probably prove most practical to select a muscle-relaxant administration technique that minimizes variation in the level of NMB (e.g., a servocontrolled infusion of relaxant); however, because the amplitude of the tc^e-MER is proportional to the amplitude of the M-response, the present results suggest that it may be feasible to use the M-response to "calibrate" the tc^e-MER to permit interpretation of the tc^e-MER amplitude when tc^e-MERs are recorded during fluctuating levels of NMB.

These observations may have considerable clinical significance, because complete omission of NMB for the purpose of tc^e-MER monitoring presents several limitations. First, as noted previously, surgical exposure may be difficult with an anesthetic regimen that uses neither volatile anesthetics nor muscle relaxants. Second, the gross movement elicited by transcranial stimulation is frequently such that the surgeon must temporarily interrupt his dissection and withdraw his instruments from the field. Third, during anesthesia with a nitrous oxide/opioid technique without NMB, there is a risk of unexpected patient movement with the attendant hazard of neurologic damage. A final disadvantage of complete absence of NMB is that spontaneous electromyographic activity may interfere with concurrent acquisition of SSERs, resulting in longer averaging times and "noisier" SSER waveforms.

Despite the admonition by some that muscle relaxants must be omitted when motor evoked responses are to be recorded (5), tc^e-MERs have been recorded during partial NMB in two previous clinical studies. Edmonds et al. (7) were able to obtain tc^e-MERs to transcranial magnetic stimulation in 9 of 11 patients during scoliosis surgery. They maintained 75%–90% NMB, as assessed by the integrated electromyographic hypothenar response to TOF ulnar nerve stimulation by giving repeated bolus doses of various NMB drugs. Calancie et al. (3) studied the effect of the introduction of isoflurane during a nitrous oxide/opioid anesthetic technique on tc^e-MER. They attempted to maintain NMB with vecuronium or atracurium at a level that retained at least two twitches to TOF stimulation. They reported that the amplitude of the M-response was typically 10%–20% of the unblocked amplitude for the first stimulus pulse. In neither study were the tc^e-MERs recorded before administration of neuromuscular blocking drugs, and as a result the relationship between level of NMB and tc^e-MER amplitude could not be completely evaluated. In ketamine-anesthetized monkeys, administration of vecuronium did not significantly decrease the opponens pollicis tc^e-MER to magnetic transcranial stimulation until M-response amplitude of the same muscle was decreased to 20% of control (8).

Our observation that the M-response persisted when the mechanical TOF response had been abolished is consistent with the findings of others. Although there is an excellent correlation between TOF ratios measured by accelerometry and mechanical force transducers (9,10), these mechanical responses have been shown previously to be more easily abolished by nondepolarizing neuromuscular blockers than the (electromyographic) M-response (11,12). Nonetheless, it is possible that a difference in sensitivity to vecuronium-induced NMB between the adductor pollicis and tibialis anterior muscle may have contributed to the relative robustness of the M-response (recorded only from the latter) during NMB. It is well known that there are major differences in sensitivity to neuromuscular blocking drugs between various muscle groups. A distal muscle such as the adductor pollicis is relatively sensitive, whereas the diaphragm is the most resistant to nondepolarizing neuromuscular blockers (13). However, Sopher et al. (14) found no difference in sensitivity to vecuronium-induced NMB, as measured by integrated electromyography between the adductor pollicis (ulnar nerve stimulation) and flexor hallucis brevis (posterior tibial nerve stimulation). We are not aware of any studies in which the tibialis anterior CMAP was compared with adductor pollicis CMAP during nondepolarizing NMB. Accordingly, we cannot completely discount the possibility that the tibialis anterior muscle is somewhat more resistant to the effects of vecuronium than the muscles of the thenar eminence.

In summary, we have demonstrated that tc^e-MERs can be recorded during anesthesia with nitrous oxide and a continuous infusion of sufentanil in the presence of clinically relevant levels of NMB, as measured by adductor pollicis accelerometry. At a T1 twitch height of 5%–15%, the reduction of tc^e-MER amplitude is 50%–60%. Provided that baseline (prerelaxant) tc^e-MER amplitude is $>150\ \mu V$, tc^e-MER monitoring should be feasible without the need for signal averaging, although simultaneous recording of the M-response will be required to permit interpretation of variations in the tc^e-MER amplitude.

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Effects of Isoflurane on K^+ and Ca^{2+} Conductance in Isolated Smooth Muscle Cells of Canine Cerebral Arteries

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Although isoflurane is a known cerebral vasodilator, the mechanism of isoflurane-induced vasodilation is not clear. The purpose of this study was to investigate the effects of 2.6% isoflurane (1.2 mM) on macroscopic calcium and potassium channel currents in voltage-clamped canine middle cerebral artery cells. Cells were dialyzed with K^+-glutamate solution and superfused with Tyrode's solution for measurement of potassium current ($n = 20$). Stepwise depolarization from a holding potential of −60 mV to beyond −30 mV elicited an outward, slowly inactivating potassium current that was reduced 50% ± 2% and 81% ± 3% (mean ± SEM) in the presence of 1 mM 4-aminopyridine and 30 mM tetraethylammonium, respectively. Calcium ionophore (A23187, 10 μM) increased the potassium current by 76% ± 3%, suggesting calcium dependency. Isoflurane reduced the amplitude of the potassium current by 35% ± 4%. Calcium current was measured in cells dialyzed with solution containing 130 mM Cs^+-glutamate and superfused with solution containing 10 mM $BaCl_2$ and 135 mM tetraethylammonium to pharmacologically isolate the calcium current ($n = 13$). Under these conditions, progressive depolarizing steps from −60 mV elicited an inward current that was maximally activated at +20 mV and essentially eliminated by 1 μM nifedipine. This current, resembling a long-lasting (L-type) Ca^{2+} channel current, was reduced 40% ± 4% by isoflurane. The results of this study suggest that isoflurane acts directly at the vascular muscle membrane to suppress transmembrane calcium and potassium currents. The decrease in calcium current would cause vasodilation; however, the concomitant decrease in potassium current may partially antagonize the depressant effect of isoflurane mediated through calcium current reduction. These effects, in interaction with other factors, may play an important role in isoflurane-induced changes of cerebral arterial tone.

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Volatile anesthetics alter cerebral blood flow in many animal species (1–3), as well as in humans (4,5). At the level of the cerebral vascular membrane, isoflurane may dilate cerebral arteries by altering ion channel behavior. This hypothesis has not yet been tested, and there is no study reporting the effects of any of the inhaled anesthetics on membrane currents in vascular smooth muscle.

Arterial smooth muscle tone is regulated by membrane potential that is determined primarily by voltage-dependent Ca^{2+} influx (6). Inward current through two types of Ca^{2+} channels has been identified in vascular smooth muscle cell membranes (7). The transient (T-type) Ca^{2+} current activates at more negative membrane potentials and decays rapidly, whereas the long-lasting (L-type) Ca^{2+} current activates at more positive membrane potentials and decays slowly. Calcium channels play an important role in electromechanical coupling in cerebral arteries, because the cerebral vasculature depends primarily on Ca^{2+} influx to increase cytoplasmic Ca^{2+} and to activate contractile proteins during contraction (8).

Different types of K^+ channels have also been described in vascular smooth muscle membranes (9). In the cerebral circulation, a 4-aminopyridine (4-AP)-sensitive, voltage-dependent K^+ current has been described in cat middle cerebral arterial cells (10). The common role of these K^+ channel currents is to control vascular muscle cell excitability. Activation of K^+ channels will cause membrane hyperpolarization, reducing the influx of Ca^{2+} through voltage-dependent Ca^{2+} channels and inducing vascular relaxation. The K^+ channels therefore act as an endogenous dilating mechanism to regulate vascular muscle tone (11).

The effects of isoflurane on K^+ and Ca^{2+} channel currents in vascular smooth muscle cells have not

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been studied. Very little is also known about ionic currents in cerebral arterial smooth muscle. Because there are significant differences among different vascular beds with regard to the physiologic properties of K^+ and Ca^{2+} currents, the purpose of this study was to characterize K^+ and Ca^{2+} channel currents in canine middle cerebral arterial muscle cells and to use the voltage-clamp method to measure directly the effects of isoflurane on these currents. Our hypothesis was that isoflurane causes cerebral vasodilation by reducing the amplitude of the Ca^{2+} channel current or increasing that of the K^+ current, or both, at the vascular muscle membrane. However, results of this study show that isoflurane suppresses the amplitude of both K^+ and Ca^{2+} channel currents in cerebral arterial cells. Because K^+ channel block favors vascular constriction and Ca^{2+} channel suppression causes vascular dilation, the direct effects of isoflurane on the vascular muscle membrane may result in electromechanical uncoupling of vascular muscle, as previously reported with halothane in the cat middle cerebral artery (12).

Methods

After approval by the Institutional Animal Care Committee, 25 adult mongrel dogs weighing 15–25 kg were placed in a Plexiglas box and anesthetized with halothane. After attainment of surgical anesthesia, brains were removed and the middle cerebral arteries were dissected free of arachnoid and placed in a chamber containing cold Krebs' solution. Any remaining blood was cleared from the arteries, and arteries were cut into 1–2-mm rings. These were placed in an enzyme solution containing NaCl 136 mM, KCl 6.0 mM, $MgCl_2$ 1.0 mM, HEPES 10 mM, $CaCl_2$ 0.5 mM, glucose 10 mM, collagenase CLS II 500 U/mL (Worthington Co., Freehold, N.J.), dithiothreitol 4 mM (Sigma Chemical Co., St. Louis, Mo.) and papain 2 U/mL (Worthington Co.). The enzyme solution was maintained at 37°C in a water bath and stirred at 5 rpm by a microstirrer (Micro-Stir, Wheaton Instruments, Millville, N.J.). After 1–2 h, the vascular pieces were disrupted mechanically by forcing them repeatedly through a Pasteur's pipette. The cell suspension was pelleted by centrifugation at 900 rpm for 8 min. The pellet was resuspended in enzyme-free solution and placed on ice. Experiments were initiated immediately.

A drop of dispersed single arterial cells was placed in a perfusion chamber (22°C) on the stage of an inverted microscope (Olympus IMT-2, Leeds Instruments, Minneapolis, Minn.) equipped with modulation contrast. At 500× magnification, a hydraulic micromanipulator (Narishige, Tokyo, Japan) was used to position heat-polished borosilicate patch pipettes with tip resistances of 4–6 MΩ on the membranes of elongated single cerebral smooth muscle cells. High-resistance seals (3–30 GΩ) were formed, after which the pipette patch was removed by negative pressure to give electrical access to the whole cell, as previously described (13). Whole-cell currents were elicited by 200-ms depolarizing pulses generated every 5–10 s by a computerized system (Pclamp software, Axon Instruments, Burlingame, Calif.). The currents were amplified by a List EPC-7 patch-clamp amplifier (Adams & List Assoc., Great Neck, N.Y.), and the amplifier output was low-pass filtered at 500 Hz. All data were digitized (sampling rate 10,000/s) and stored on a hard disk to permit analysis at a later time. Leak and capacitative currents were subtracted from each record by linearly summating scaled currents obtained during 10-mV hyperpolarizing pulses.

The external solution used for measuring K^+ currents contained $CaCl_2$ 2.0 mM, NaCl 135 mM, KCl 4.7 mM, $MgCl_2$ 1.0 mM, glucose 10 mM, and HEPES 5 mM (pH 7.4). The pipette solution contained K^+-glutamate 130 mM, $MgCl_2$ 1.0 mM, EGTA 1.0 mM, HEPES 10 mM, and Na_2-ATP 3.0 mM (pH 7.1–7.2). The external solution used for Ca^{2+} current measurement consisted of $BaCl_2$ 10 mM, tetraethylammonium (TEA) chloride 135 mM, $MgCl_2$ 1.0 mM, glucose 10 mM, and HEPES 10 mM (pH 7.4). In the pipette solution, Cs^+ was substituted for K^+ to eliminate the K^+ current and permit isolated measurement of the Ca^{2+} current.

Repetitive current-voltage curves were obtained in the control solution to monitor time-dependent changes in K^+ current. Only cells with stable current amplitudes were exposed to isoflurane or other drugs to study their effects. After steady-state effect was established by repetitive measurements, the inflow perfusate was changed to one containing isoflurane or other drugs. Isoflurane effects were complete within 2 min. Isoflurane produced reversible decreases in K^+ currents that were verified by obtaining measurements after removal of isoflurane from the perfusate. Calcium current measurements were complicated by a time-dependent decay in the current amplitude. To circumvent this problem of Ca^{2+} current "rundown," cells for Ca^{2+} current measurement were exposed to control and isoflurane-containing solutions in random order. This protocol consisted of control measurements, followed by a second set of measurements after 3-min exposure to isoflurane. In another group of cells, measurements of Ca^{2+} current were made during isoflurane exposure, followed by control measurements after a washout period of 3 min. The solution was sampled from the perfusion chamber and analyzed by gas chromatography to verify the anesthetic concentration at the cell proximity (14). The average bath concentration of isoflurane was 1.2 ± 0.02 mM (mean ± SEM), which was calculated to correspond to 2.6 vol%. This is based on a partial pressure of 1 vol% of isoflurane, which is equivalent to a concentration of 0.46 mM in Krebs-Ringer's solution at 22°C at a pressure of 1 atm (15). Nifedipine (Sigma) was dissolved in 70% ethanol to make a 1.0-mM stock solution. The final concentration of solvent in the recording solution was 0.07%. 4-Aminopyridine (Sigma) was dissolved directly in the recording solutions. When TEA (Sigma) was used, it was substituted for Na^+ in the external solution in an equimolar concentration. The Ca^{2+} ionophore A23187 (Boehringer Mannheim GmbH, Mannheim, Germany) was dissolved in dimethyl sulfoxide at a stock concentration of 10 mM, stored at 0°C, and diluted into the extracellular solution (Tyrode's) to a final concentration of 10 μM before use. At concentrations used, solvents did not significantly alter these currents.

All currents are expressed as mean ± SEM and were analyzed by a two-way analysis of variance. If the F-test showed significance, Fisher's exact test for least significant difference was performed, with the level of significance at $P \leq 0.05$.

Results

Cells dialyzed with high-K^+ solution showed outward currents during the 200-ms depolarizing steps, changing from a holding potential of −60 mV to potentials more positive than −30 mV. This current was eliminated when Cs^+ was substituted for K^+ in the pipette solution, indicating that K^+ was probably the mandatory charge carrier for this current (16). With cell depolarization, an increasing amplitude of oscillatory current was evident to various degrees in different cells (Figure 1A). This current has been previously shown to be dependent on intracellular Ca^{2+} release (17). To better characterize the TEA-insensitive K^+ current (I_K), cells were exposed to increasing concentrations of TEA (1, 10, and 30 mM) in the external solution. Figure 1A shows the suppression of peak I_K in a single cell by increasing concentrations of TEA. Figure 1B illustrates the effect of TEA on the current-voltage relationship for K^+ channel activation ($n = 4$). Concentrations of 1, 10, and 30 mM of TEA dose-dependently reduced I_K elicited by depolarization from −60 to +60 mV to 75% ± 4%, 53% ± 3%, and 19% ± 3% of the control amplitude (622 ± 131 pA), respectively. This depression was evident at all voltages studied, and the depressant effect of TEA on I_K was completely reversible on washout.

4-Aminopyridine was a potent antagonist of the outward I_K. Figure 2A shows that concentrations of 0.1 and 1 mM 4-AP caused a dose-dependent depression of macroscopic I_K in a single cell. The effect of 4-AP on the current-voltage relationship for K^+ channel activation is shown in Figure 2B ($n = 4$). 4-Aminopyridine (0.1 and 1 mM) reduced I_K (elicited by voltage steps from −60 to +60 mV) to 75% ± 5% and 50% ± 2% of control, respectively. Therefore, 4-AP was more potent than TEA in depressing I_K.

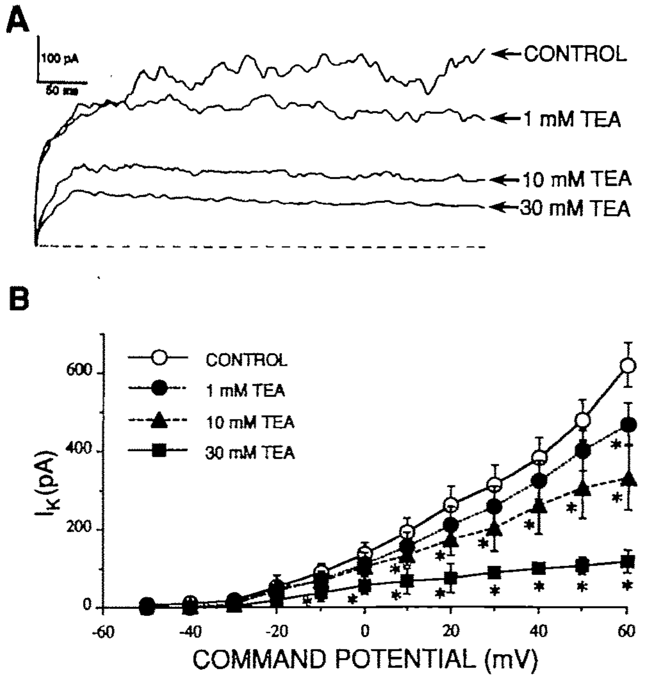

Figure 1. (A) Effects of increasing concentrations of tetraethylammonium chloride (TEA) on K^+ outward current (I_K) elicited by depolarizing pulses from a holding potential of −60 to +60 mV in one cell. (B) The current-voltage relationship for I_K activation in control solution and in the presence of TEA. TEA reduced I_K amplitude in a concentration-dependent manner throughout the entire voltage range studied. Data are mean ± SEM; $n = 4$. $*P \leq 0.05$ versus control.

In many smooth muscle cells, the major outward current in response to membrane depolarization is carried by Ca^{2+}-activated K^+ channels (18–22). To determine whether I_K in cerebral arterial cells was dependent on intracellular Ca^{2+} concentrations, I_K amplitude was measured in control (Tyrode's) solution and again after the addition of 10 μM Ca^{2+} ionophore (A23187). A23187 increases intracellular Ca^{2+} concentration by binding to the Ca^{2+} ion and conferring membrane permeability (23). Figure 3A illustrates increases in peak amplitude of I_K by 10 μM A23187 added to the external solution in one cell. A23187 increased I_K by 76% ± 3% (from control peak current 459 ± 74 pA to 808 ± 87 pA) and enhanced the entire current-voltage relationship for I_K (Figure 3B) ($n = 6$).

The effects of 2.6% isoflurane on whole-cell I_K were determined by applying a series of test pulses from a holding potential of −60 mV to more positive voltages of up to +60 mV. Figure 4A illustrates the depressant effect of isoflurane on a series of I_K recordings in one

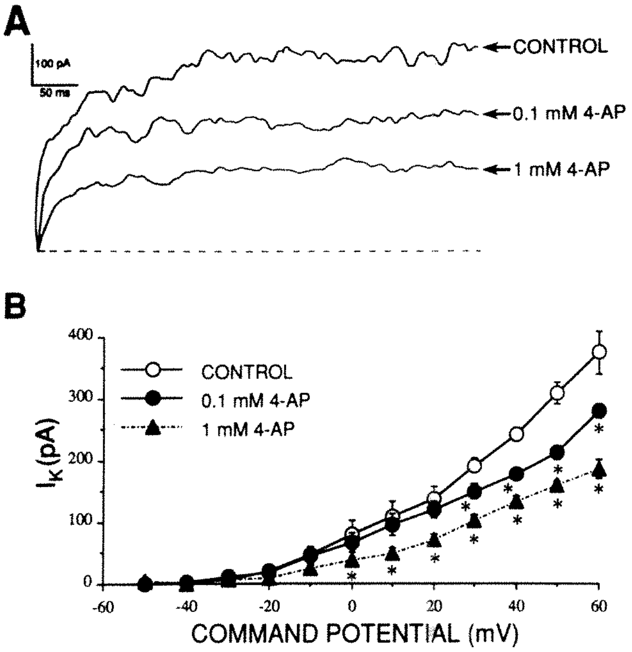

Figure 2. **(A)** Depression by 0.1 and 1 mM 4-aminopyridine (4-AP) of K^+ current (I_K) elicited by depolarization from a holding potential of −60 to +60 mV in one cell. **(B)** The control current-voltage relationship for I_K activation was depressed by 4-AP in a dose-dependent fashion at all voltages. Data are mean ± SEM; $n = 4$. $^*P \le 0.05$ versus control.

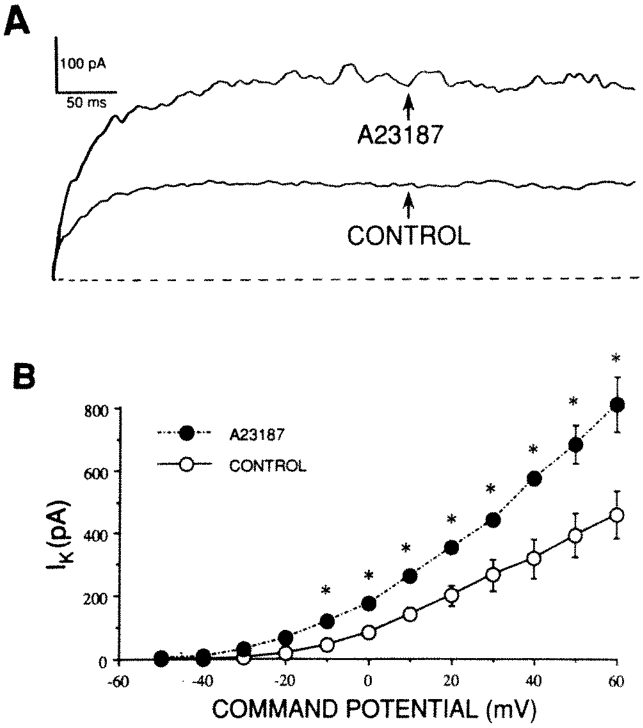

Figure 3. **(A)** Ca^{2+} dependency of K^+ outward current (I_K) was investigated by exposing canine middle cerebral arterial cells to 10 μM Ca^{2+} ionophore (A23187). The actual tracing of the effect of A23187 in the cell (which was depolarized from a holding potential of −60 to +60 mV) is shown. **(B)** The current-voltage relationship for I_K activation in control solution and in the presence of 10 μM A23187. A23187 caused significant increase in I_K, suggesting Ca^{2+} dependency. Data are mean ± SEM; $n = 6$. $^*P \le 0.05$ versus control.

cell. This effect of isoflurane on I_K was reversed completely on washout of the anesthetic agent. Peak I_K was plotted as a function of membrane potential to analyze the effect of isoflurane (Figure 4B) on the current-voltage relationship for I_K activation (expressed as percent of maximal I_K) ($n = 6$). Isoflurane decreased peak I_K amplitude throughout the voltage range studied; however, this depression was statistically significant only at voltages more positive than +40 mV.

Whole-cell Ca^{2+} current (I_{Ca}) was isolated by substituting Cs^+ for K^+ in the pipette solution and TEA for Na^+ and K^+ in the external solution, as previously detailed (24). Calcium current was generated by stepwise depolarizing pulses lasting 200 ms from a holding potential of −60 mV to a more positive command potential of up to +60 mV with barium (Ba^{2+}) as a charge carrier. In 13 cells, inward current was detected at −10 mV, and maximal activation was reached at +20 mV. Maximal I_{Ca} amplitude varied greatly between cells (range 40–230 pA; average 123 ± 29 pA).

To further characterize the channel pathway for inward current, the effects of external nifedipine (1 μM) on I_{Ca} were measured by depolarizing cells from a holding potential of −60 mV to more positive voltages of up to +60 mV. Both Ba^{2+} and nifedipine act more selectively on the L-type than the T-type Ca^{2+} channel, the former being a preferential charge carrier and the latter a specific blocker of the L-type channel (7). Nifedipine nearly abolished the I_{Ca} in a cell shown in Figure 5A. Using the same pulsing protocol, 1 μM nifedipine reduced the entire current-voltage relationship for Ca^{2+} channel activation, reducing maximal current to 17% ± 2% of the original amplitude (Figure 5B) ($n = 5$).

Administration of 2.6% isoflurane depressed I_{Ca} amplitude at all voltages studied, as shown in Figure 6A. Isoflurane decreased the entire current-voltage curve for Ca^{2+} channel activation (expressed as percent of maximal I_{Ca}). Isoflurane decreased peak I_{Ca} by 40% ± 4% from peak control current (123 ± 29 pA) (Figure 6B) ($n = 8$). This effect of isoflurane was not voltage dependent (i.e., no shift in the current-voltage relationship was observed). The isoflurane curve, when scaled up to match the control curve at maximal amplitude, was not significantly different from the control curve, supporting the conclusion that the effect of isoflurane was not voltage dependent.

Discussion

The effects of isoflurane on cerebral blood flow (CBF) have been examined in a number of studies. The

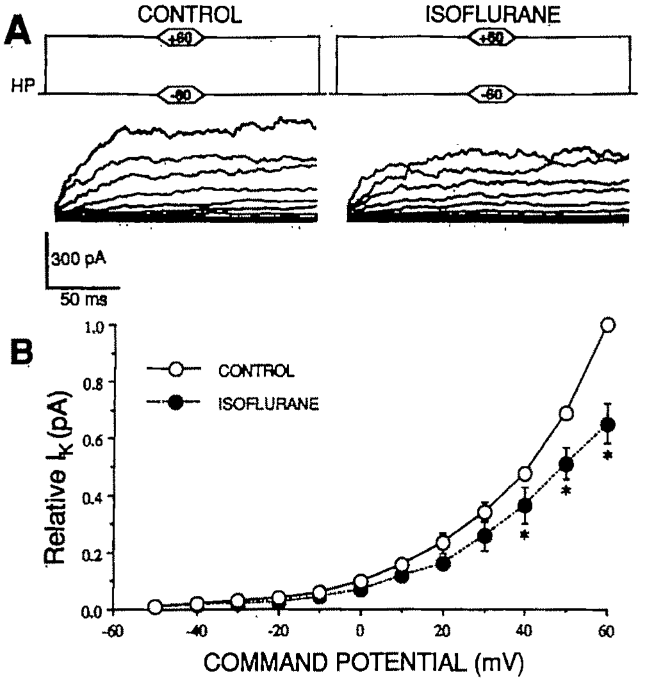

Figure 4. (A) Effect of 2.6% isoflurane on K^+ current (I_K) elicited by progressive 10-mV test pulses from −60 to +60 mV in one cell. (B) The current-voltage relationship for I_K activation in control solution and in the presence of isoflurane. Isoflurane significantly depressed I_K amplitude only at the most positive voltages studied. Data are mean ± SEM; $n = 6$. $^*P \leq 0.05$ versus control. HP, holding potential.

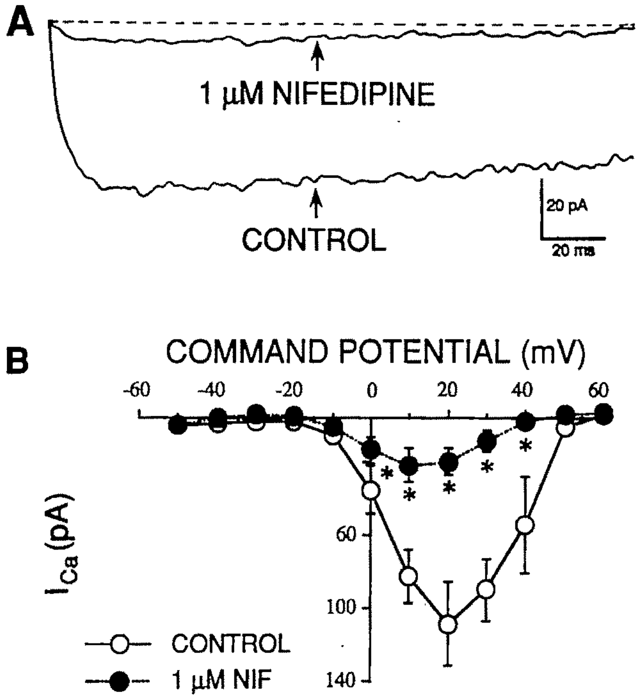

Figure 5. (A) Cells dialyzed with Cs^+-containing solution and superfused with 10 mM Ba^{2+} showed inward currents when depolarized from a holding potential of −60 mV to potentials positive to −10 mV, with maximal current activated at +20 mV. The effects of 1 μM nifedipine on peak Ca^{2+} current (I_{Ca}) elicited by depolarizing pulses from −60 to +20 mV are shown. I_{Ca} was almost completely blocked by 1 μM nifedipine. (B) The peak current-voltage relationship for I_{Ca} activation in the control solution and in the presence of 1 μM nifedipine. Data are mean ± SEM; $n = 5$. $^*P \leq 0.05$ versus control.

general conclusion is that isoflurane causes an increased ratio of oxygen supply to demand by increasing CBF caused by cerebral dilation (2,25,26) and decreasing the cerebral metabolic rate (CMR) (2). Compared with other vascular beds, large cerebral arteries play an important role in regulating total cerebral vascular resistance (27). Therefore the effects of isoflurane on the diameter of these vessels may induce significant changes in blood flow. However, it is unclear how alterations in cerebral metabolism, endothelium-derived factors, vasoactive neurotransmitters, and hormones interact with the direct action of isoflurane on the vascular muscle membrane to cause dilation. Isoflurane-induced dilation in vivo probably involves actions other than a purely direct vascular effect, because increases in CBF are accompanied by a depressed CMR (1,3). The increase in CBF concurrent with a reduced CMR suggests uncoupling between these otherwise very closely coupled variables.

In vitro, isoflurane has also been shown to be a potent dilator of cerebral arteries (28). In general, contractile mechanisms in cerebral blood vessels appear to be more dependent on extracellular Ca^{2+} influx than on intracellular stores of Ca^{2+} (8,29,30). For example, the Ca^{2+} entry blocker nimodipine is a potent dilator of cerebral vessels but has a smaller effect on peripheral vessels, further supporting the hypothesis that the entry of extracellular Ca^{2+} is critical for cerebral artery contraction (8). Thus, isoflurane-induced modulation of Ca^{2+} influx would represent a potential powerful dilator mechanism.

The dilative effects of isoflurane on cerebral blood vessels have been studied with whole-brain and regional CBF (31,32). Isoflurane was found to produce regionally selective effects on CBF in rats, having a small effect on the neocortex (31) and the greatest effect on the brainstem and cerebellum (25). The effects of isoflurane on CBF depend on the preexisting CMR (33). Isoflurane is also a potent arterial dilator in other vascular beds (34–38). The mechanism of the isoflurane-induced dilative effect is probably multifactorial because isoflurane acts at different sites and in many tissues.

The purpose of this study was to identify the cellular actions of isoflurane on K^+ and Ca^{2+} channel currents in the cerebral arterial cell membrane. We found that isoflurane reduced the amplitude of K^+ and Ca^{2+} channel currents in the vascular muscle

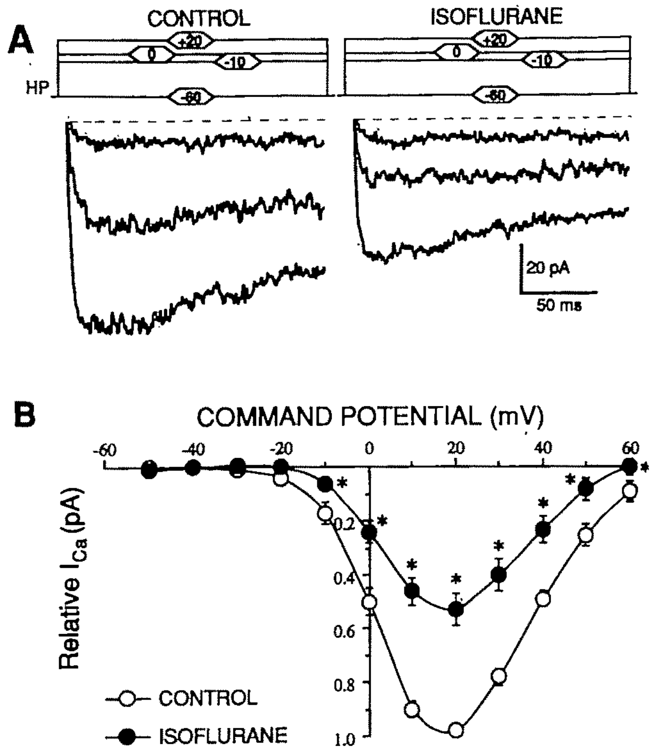

Figure 6. (A) Recordings of Ca^{2+} current (I_{Ca}) generated by progressive (10-mV increments) depolarizing pulses from −60 mV to more positive membrane potentials (up to +60 mV). Only selected episodes are shown: −60 mV (*dashed line*, holding potential, [HP]) and −10, 0, and +20 mV. Measurements during control and isoflurane were randomized to circumvent the problem of I_{Ca} rundown. (B) Peak I_{Ca} current-voltage relation obtained during control and exposure to isoflurane. Isoflurane significantly depressed I_{Ca} at all voltages studied. Data are mean ± SEM; $n = 8$. *$P \leq 0.05$ versus control.

membrane. Of these two channel types, isoflurane was a more potent blocker of the Ca^{2+} channel current at more negative membrane potentials. This was particularly evident at potentials more negative than −20 mV, which is within the physiologic range for smooth muscle cells, including cerebral arteries (39). These findings concur with previous voltage-clamp experiments showing anesthetic-induced suppression of K^+ and Ca^{2+} channel currents in cardiac Purkinje cells (14,40).

Data from this study suggest that in cerebral arterial muscle cells, isoflurane alters ionic fluxes through slowly inactivating, voltage-dependent K^+ channels and the long-lasting type Ca^{2+} channels. The macroscopic I_K measured in our study was more sensitive to 4-AP than to TEA. A similar 4-AP-sensitive, TEA-insensitive I_K has been described in pulmonary (11), coronary (22), and cat middle cerebral arteries (10). In our study, I_K was also sensitive to 10 μM A23187, suggesting Ca^{2+} dependence. These K^+ channels may modulate vasodilation and probably play an important role in regulating coronary artery tone (22). Activation of outward I_K causes cell hyperpolarization, inactivation of voltage-dependent Ca^{2+} channels, and subsequent arterial relaxation (41). This mechanism has been implicated in the prevention of vasospasm (41).

Two distinct Ca^{2+} channel types have been identified in smooth muscle tissues (7). The transient (T-type) current activates at more negative membrane potentials and decays rapidly, whereas the long-lasting (L-type) current activates at more positive membrane potentials and decays slowly. Unlike in cardiac Purkinje fibers (14) and mesenteric arteries (7), we were able only to identify the L-type Ca^{2+} channel in this preparation. The high threshold for Ca^{2+} channel current activation and effective block by nifedipine are consistent with the voltage-dependent and pharmacologic properties of the L-type Ca^{2+} channel (7,42). The isoflurane-induced block of this channel current would help to explain the direct dilative effect of isoflurane on cerebral vasculature. A reduction of Ca^{2+} influx would dilate cerebral arteries, which rely predominantly on the influx of external Ca^{2+} for the maintenance of contraction (8,30). On the other hand, the simultaneous block of K^+ channel current by isoflurane would favor membrane depolarization, because K^+ conductance is crucial for repolarization of cell membrane potential and cerebral arterial relaxation. Although this membrane depolarization may initially open voltage-dependent Ca^{2+} channels in the vascular membrane, the effective block of Ca^{2+} influx by isoflurane would probably minimize the contribution of these channels to the cytoplasmic Ca^{2+} concentration.

Taken together, the simultaneous depression of I_K and I_{Ca} by isoflurane would suggest that isoflurane could cause electromechanical uncoupling of cerebral vascular smooth muscle. The predominant action of isoflurane to reduce Ca^{2+} influx would coincide with membrane depolarization mediated by isoflurane suppression of K^+ permeability, permitting vascular relaxation coincident with membrane depolarization. This uncoupling has been demonstrated previously during exposure of cat cerebral arteries to halothane (12). The results of this study suggest that the preferential depression of I_{Ca} by isoflurane may be one mechanism to reduce cytosolic Ca^{2+} levels in arterial cells during general anesthesia and contribute to cerebral vasodilation.

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A New Approach to Intravenous Regional Anesthesia

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In an attempt to reduce the dose of local anesthetic during intravenous (IV) regional anesthesia of the upper limb, we combined 100 mg of lidocaine with 0.05 mg of fentanyl and 0.5 mg of pancuronium. The study was designed in a randomized, double-blind fashion to determine the efficacy of this approach in providing analgesia and relaxation during surgery and to evaluate its safety after immediate deflation of the tourniquet following IV drug injection. Eighty unpremedicated patients, ASA physical status I or II, were assigned to the following groups: group A (n = 15) received 100 mg of lidocaine diluted in 40 mL of NaCl IV; groups B–D (n = 15 in each group) received 100 mg of lidocaine diluted in NaCl, with the addition of 0.05 mg of fentanyl (group B) or 0.5 mg of pancuronium (group C), or both (group D) to a total volume in all groups of 40 mL. Patients in groups A–D underwent elective operations on the forearm, wrist, and hand; for evaluation of safety, in 20 volunteers (group E) the tourniquet was immediately released after IV injection of the three drugs at the previously described doses. The analgesic effect was more profound in group D compared with groups A–C. In group D, 9 of 15 patients had excellent analgesia. In six patients, pain was experienced at the beginning of surgery, but 5 min thereafter patients remained pain free. In group B, analgesia was obtained successfully in only 26.6% of cases compared with group A with 13.3%. Skeletal muscle relaxation was profound in groups C and D compared with groups A and B. Signs indicating toxicity were not encountered after release of the tourniquet in these groups. In group E, the volunteers complained of minor events, such as mild dizziness and transient visual disturbances. In one case, vomiting and hypotension with a systolic arterial blood pressure of 90 mm Hg occurred 5 min after release of the tourniquet. In conclusion, this approach to IV regional anesthesia with the combination of lidocaine, fentanyl, and pancuronium offers adequate analgesia and relaxation during upper limb surgery.

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In intravenous (IV) regional anesthesia, with the tourniquet conventionally placed over the upper arm, a relatively large dose of local anesthetic is required to induce appropriate sensory blockade. For lidocaine, 3 mg/kg administered as a 0.5% solution ensures adequate analgesia and relaxation when used for upper limb surgery. However, toxic reactions, including convulsions, coma, cardiorespiratory depression, and even cardiac arrest have been reported (1–8). Toxicity may be due to leakage past the tourniquet after injection caused by either tourniquet failure or buildup of excessively high venous pressure distal to the tourniquet (9–11). In view of the possible central nervous system and cardiovascular toxicity, use of an alternative approach to IV regional anesthesia with fewer side effects would be desirable. Lidocaine is considered one of the least toxic local anesthetics (12) and in the usual IV dosage of 1–2 mg/kg is safe and effective for treating ventricular arrhythmias (13) or attenuating the cardiovascular response to endotracheal intubation (14). On the other hand, analgesia was insufficient when a similar dose of lidocaine administered as a 0.25% solution was used alone for IV regional anesthesia with the tourniquet placed on the upper arm (15).

Our clinical trials indicated that the addition of 0.05 mg of fentanyl and 0.5 mg of pancuronium to 100 mg of lidocaine improves the quality of analgesia and relaxation during various surgical procedures on the upper limbs. Our double-blind study was designed to establish the efficacy of this new approach to IV regional block in controlling analgesia and relaxation during surgery. Furthermore, its safety was evaluated immediately after deflation of the tourniquet following IV drug injection.

Methods

Informed consent was obtained from each patient, and the study was approved by the Hospital Human Investigation Committee. Eighty unpremedicated patients (46 male and 34 female), ASA physical status I

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or II, were assigned in a randomized, double-blind fashion to the following groups: group A ($n = 15$) received 100 mg of lidocaine diluted in 40 mL of NaCl IV; groups B–D ($n = 15$ in each group) received 100 mg of lidocaine diluted in NaCl with the addition of 0.05 mg of fentanyl (group B) or 0.5 mg of pancuronium (group C), or both (group D), to a total volume in all groups of 40 mL. In group E ($n = 20$), volunteers received 100 mg of lidocaine, 0.05 mg of fentanyl, and 0.5 mg of pancuronium, and the tourniquet was immediately released after IV injection of the drugs. Patients in groups A–D underwent various elective operations on the forearm, wrist, and hand 10 min after IV injection.

Once the patient was in the operating room, a plastic intravenous cannula (20 gauge) was inserted in a distal vein of the affected hand, preferably on the dorsum. An infusion of IV fluid was commenced on the contralateral arm on which a blood pressure cuff was also applied. A bipolar lead II of the electrocardiogram was continuously monitored from the start of the procedure. The limb was then elevated for 5 min, and an Esmarch bandage was applied from the fingers proximally to reach a double-cuffed tourniquet applied on the upper arm. The proximal cuff was first inflated to 250–300 mm Hg with a constant-pressure pneumatic inflator. The Esmarch bandage was then removed, and 40 mL of a solution was injected intravenously. Once anesthesia was started in the limb, the distal cuff on the analgesic part was inflated, and the proximal one was deflated. Surgery was begun 10 min after injection of the drugs in groups A–D, whereas the tourniquet was immediately released after injection of the drugs in group E. All patients were monitored in the standard manner.

Intraoperative degree of analgesia was evaluated by the patient as well as by an observer using two different pain scores (16,17). Scores were assigned to the patient at 5-min intervals during surgery (Table 1). The subjective pain score (17) was explained to each patient on the day before surgery. To enhance its sensitivity, key descriptive phrases and pictures depicting facial expressions of pain or its absence were associated with the numbers on the score. For example, a 10 on the score was described as "pain is excruciating," whereas 0 was described as "no pain," with the midsection labeled as "moderate." Patients were instructed on the use of numerical responses to standard questions that would be asked of them with regard to skin incision and closure and intraoperative levels of pain associated with the surgical area. These instructions were reinforced preoperatively by the anesthesia staff on the day of surgery. Although different staff interviewed the patients, all instructions and questions were standardized.

Table 1. Objective Pain Scoring System

Score	Description	Feature
0	Excellent	Patient was completely pain free and lying quietly
1	Good	Patient was satisfied but experienced minor pain for a short period during surgery
2	Incomplete	Patient had significant pain relief but experienced minor pain during most of the time of surgery
3	Failure	Patient had no pain relief during most of the time of surgery
4	Excruciating	Surgery under general anesthesia

Sensation was tested by multiple pinpricks on the affected arm and by monitoring of neuromuscular blockade using train-of-four stimulation by applying four supramaximal stimuli (2 Hz) at intervals of 0.5 s over a period of 2 s at the ulnar nerve with surface electrodes. Complete neuromuscular blockade was determined by the disappearance of muscle twitch responses to train-of-four stimulation and was assessed by tactile and visual evaluation without recording equipment.

Testing for statistical significance was done using two-factor analysis of variance followed by the Mann-Whitney test and χ^2 analysis. A P value < 0.05 was considered significant.

Results

In all groups, there were no significant differences in age, body weight, height, gender, and general health. Likewise, surgical procedures performed on forearm, wrist, and hand in groups A–D were similar in type and included soft tissues, nerves, tendons, bone, and joints (Table 2). In addition, no significant difference in injection-release interval was found.

Intraoperative degree of analgesia was assessed similarly by the patient and the observer (Table 3, Figure 1). The analgesic effect was significant in group D compared with groups A–C. In 9 of 15 patients, analgesia was excellent. In six patients, minor pain was experienced only after start of surgery, and for 5 min thereafter patients were pain free and remained so 10 min postoperatively (Table 3). Pain sensation to pinprick in group D was abolished 5–10 min after drug injection and returned immediately after release of the tourniquet. In group A, analgesia was good in only two subjects and was incomplete in two others. Analgesia failed in eight subjects, mainly 10 min after start of surgery. Three subjects were changed to general anesthesia, two of them 10 min and the third 15 min after start of surgery owing to excruciating pain that could not be

Table 2. Clinical Characteristics of the Five Study Groups

	Group A (n = 15)	Group B (n = 15)	Group C (n = 15)	Group D (n = 15)	Group E (n = 20)
Gender (M/F)	8/7	9/6	10/5	9/6	10/10
Age (yr)	36 ± 18	34 ± 17	38 ± 18	40 ± 21	40 ± 17
Weight (kg)	64 ± 11	69 ± 12	67 ± 13	69 ± 10	62 ± 10
Height (cm)	163 ± 7	168 ± 11	163 ± 10	168 ± 8	164 ± 10
Duration of ischemia (min)	32 ± 11	31 ± 9	34 ± 13	36 ± 13	—
Operation (No./type)	4/Excision of ganglion 3/Wound excision 1/Removal of foreign body 2/Bone graft 2/Amputation 1/Fracture fixation 2/Manipulation	2/Excision of ganglion 3/Wound excision 2/Mass excision 1/Release of carpal tunnel 2/Amputation 2/Repair of tendon 3/Manipulation	2/Excision of ganglion 3/Wound excision 1/Removal of foreign body 1/Drainage of abscess 1/Fracture fixation 2/Release of contracture 2/Wrist exploration 1/Tendon transfer 2/Manipulation	3/Excision of ganglion 3/Wound excision 1/Mass excision 1/Bone graft 2/Amputation 1/Fracture fixation 2/Repair of tendon 1/Wrist exploration 1/Manipulation	

M, male; F, female.
Mean ± SD.

Table 3. Objective Assessment of Level of Analgesia in Four Study Groups

Study group[a]	Level of analgesia					Successful analgesia [No. (%)]
	Excellent	Good	Incomplete	Failure	Excruciating	
A	0	2	2	8	3	2 (13.3)
B	0	4	1	8	2	4 (26.6)
C	0	1	7	5	2	1 (6.6)
D	9	6	0	0	0	15 (100)

[a] n = 15 in each group.

tolerated. In group B, analgesia was obtained successfully in 26.6% of subjects (Table 3). Analgesia was complete in four patients, and one patient with incomplete analgesia experienced minor pain during most of the surgery. Failure of analgesia was reported in eight cases, and general anesthesia was initiated in two patients 10–15 min after start of surgery. In group C, good analgesia was achieved in only one subject; it was incomplete in seven and failed in five others. In two patients, general anesthesia was necessary (Table 3). Operations on patients who had little pain relief for most of the surgery could be completed under IV block with the help of 5–10 mg of diazepam with or without IV meperidine. Neuromuscular blockade was profound in groups C and D compared with groups A and B. Complete abolition of twitch response and absence of spontaneous movements on command in groups C and D were achieved within 4–5 min after drug injection. Muscle power returned within 5–10 min after release of tourniquet.

With regard to safety, questioning of patients undergoing surgery did not reveal any toxic symptoms. In group E, all volunteers complained of mild dizziness; four developed visual disturbances starting 1 min and lasting 5–7 min after the release of the tourniquet. In another volunteer, vomiting and hypotension with systolic arterial blood pressure of 90 mm Hg occurred 5 min after release of tourniquet and returned to normal 5 min later without any IV fluid or drug administration. This volunteer's hemoglobin was 8.6 g/dL. In six subjects, there was some difficulty in moving the affected arm. This disappeared within 15 min. Another subject experienced heaviness in the eyelids and had difficulty opening his eyes. Sinus tachycardia developed in five subjects at 2 min and subsided by itself 5–10 min after release of tourniquet. In other five subjects, tachypnea was recorded 2 min after release of tourniquet and subsided 10 min later, except in one volunteer who remained tachypneic for 20 min and had chronic bronchitis and emphysema.

Discussion

Our preliminary investigation demonstrates the efficacy of the modified IV block developed at our institution, with the tourniquet conventionally placed

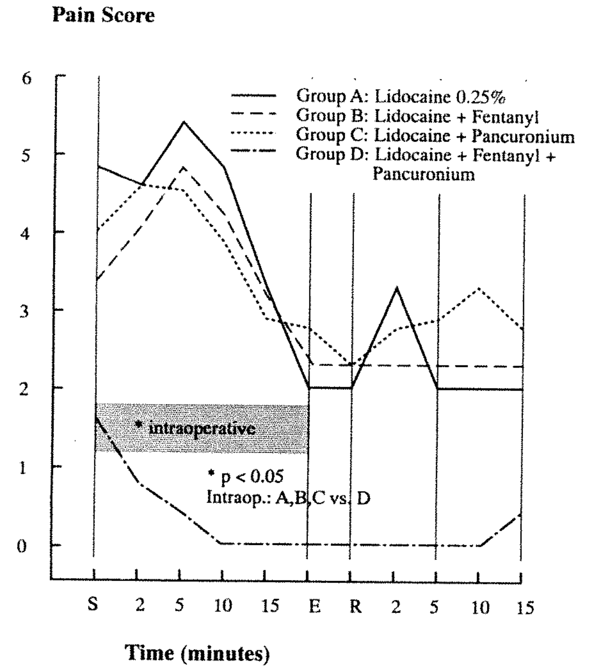

Figure 1. Subjective pain assessment in study groups A–D. R, release of tourniquet. E, end of surgery; S, start of surgery.

over the upper arm and with a dose of lidocaine comparable to the size of the bolus dose used for treating ventricular arrhythmias (13) or before endotracheal intubation (14). Analysis of data shows that the differences among the groups were clearly significant in group D. The patients rated their analgesia as good or excellent, and successful analgesia was achieved with a dose of no more than 100 mg of lidocaine. So far, adequate analgesia has been observed only with 0.5% lidocaine, suggesting that more dilute solutions do not appear to provide adequate analgesia (8,12,15). Accordingly, in group A with 0.25% lidocaine, heavy sedation or general anesthesia was required in eight patients. This high failure rate may have been reduced if our patients had been premedicated. The addition of 0.05 mg of fentanyl in group B significantly increased the quality of analgesia compared with group A, preserving the benefit of a low dose of local anesthetic. An additional advantage noted in our study using an upper arm tourniquet was complete muscle relaxation, which was very useful in certain operations such as those for tendolysis and proper fixation of bone fractures. The regional administration of muscle relaxants has been used for experimental, therapeutic, and diagnostic purposes (18,19).

The possible mechanism by which fentanyl enhances the action of lidocaine on peripheral nerve blockade is unclear. Although no in vivo studies have demonstrated a measurable local anesthetic effect of fentanyl, in vitro studies have shown that perineural fentanyl depresses the action potential in nerve fibers of different types (20,21). Recordings of fast-conducting A fibers and slow-conducting C fibers before and after exposure to 50 and 100 μg/mL of fentanyl indicate that a high concentration of fentanyl may partially suppress conduction in peripheral nerves and apparently does not diffuse well through a nerve sheath (20). Thus, it is unlikely that fentanyl per se would cause conduction blockade in vivo in peripheral nerves that are enclosed within a nerve sheath. Opioids are much more effective at blocking dull pain (C fibers) than acute pain (A-delta fibers). This agrees with the observation that the addition of fentanyl (50 μg/mL) to stable bupivacaine block significantly augments the effect, particularly of C fibers (21). Thus, labor and surgical pain are not completely blocked by opioids alone. The depressant effect of fentanyl on the action potential of A and C fibers in desheathed peripheral nerves is probably not related to the presence of opiate receptors in these nerves, because pretreatment with naloxone failed to inhibit the decrease in action potential produced by fentanyl (20). This also agrees with the observation that there is a virtual absence of opiate receptors in spinal ventral roots and in peripheral nerves (22). In this regard, evidence has been presented by various investigators that opiates may have a dual mechanism of action (23,24). The primary clinical effect is related to interaction with opiate receptors after epidural or intrathecal administration. On the other hand, fentanyl may cause some depression of nerve transmission similar to that produced by local anesthetics. This fact suggests that fentanyl may possess weak local anesthetic properties. It is possible that the addition of local anesthetics to fentanyl enhances its weak local anesthetic effect to such an extent that a clinical response can be observed as in group B. The success rate in group B would probably have been even higher in premedicated patients. However, the combination of the three drugs used in group D in our study improved the quality of analgesia and relaxation in such a way that upper limb surgery could be accomplished with success in all cases.

The safety of this modification was confirmed in group E by the absence of serious symptoms and signs of toxicity after release of tourniquet pressure immediately after injection of the drugs. In group E, only mild side effects attributable to the technique were noted. One person complained of transient hypotension associated with nausea after immediate deflation of the tourniquet. Thus, the low lidocaine dose used in group D represents a negligible risk in the event of accidental release of tourniquet pressure, with a further decreased risk with the addition of fentanyl and pancuronium, owing to the smaller dose of lidocaine used.

Therefore the combination of these drugs may prove to be a useful adjunct to IV regional anesthesia.

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A Comparative Study of 0.25% Ropivacaine and 0.25% Bupivacaine for Brachial Plexus Block

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The present study compares the effectiveness of 0.25% ropivacaine and 0.25% bupivacaine in 44 patients receiving a subclavian perivascular brachial plexus block for upper extremity surgery. The patients were assigned to two equal groups in this randomized, double-blind study; one group received ropivacaine 0.25% (112.5 mg) and the other, bupivacaine 0.25% (112.5 mg), both without epinephrine. Onset times for analgesia and anesthesia in each of the C-5 through T-1 brachial plexus dermatomes did not differ significantly between the two groups. The mean onset time for analgesia ranged from 11.2 to 20.2 min, and the mean onset time for anesthesia ranged from 23.3 to 48.2 min. The onset of motor block differed only with respect to paresis in the hand, with bupivacaine demonstrating a shorter onset time than ropivacaine. The duration of sensory and motor block also was not significantly different between the two groups. The mean duration of analgesia ranged from 9.2 to 13.0 h, and the mean duration of anesthesia ranged from 5.0 to 10.2 h. Both groups required supplementation with peripheral nerve blocks or general anesthesia in a large number of cases, with 9 of the 22 patients in the bupivacaine group and 8 of the 22 patients in the ropivacaine group requiring supplementation to allow surgery to begin. In view of the frequent need for supplementation noted with both 0.25% ropivacaine and 0.25% bupivacaine, we do not recommend using the 0.25% concentrations of these local anesthetics to provide brachial plexus block.

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Ropivacaine is a new long-acting local anesthetic that is a chemical congener of bupivacaine and mepivacaine. In the initial studies in humans, 0.5% ropivacaine, both with and without epinephrine, provided effective sensory and motor blockade when used to provide brachial plexus anesthesia (1). More recently, a double-blind comparison of 0.5% ropivacaine with 0.5% bupivacaine demonstrated the two drugs to be similar in terms of both onset and duration of sensory and motor block and in terms of the incidence of analgesia, anesthesia, paresis, and paralysis (2).

Both bupivacaine and mepivacaine contain a chiral center and thus can exist as a pair of stereoisomers or enantiomers, currently designated as either *R*- or *S*-configurations (3). Nonetheless, both of these local anesthetics are prepared and used clinically as the racemate despite differences in the pharmacodynamics and pharmacokinetics of such enantiomers. The *S*-enantiomer is the principal agonist (the eutomer), because it possesses true local anesthetic activity, whereas the *R*-enantiomer (the distomer) not only possesses less local anesthetic activity, but greater toxicity (4–7). When ropivacaine, a congener of mepivacaine and bupivacaine, was considered as a replacement for bupivacaine in regional anesthesia, it was made available as the pure *S*-enantiomer, the assumption being that the use of the *S*-enantiomer would provide greater local anesthetic potency and less local anesthetic toxicity than the racemic mixture. Subsequently, animal data have indicated that ropivacaine does possess anesthetic properties that are very similar to those of its racemic relative, bupivacaine, but with considerably less anesthetic toxicity, particularly in terms of the cardiovascular system (6,7). Because ropivacaine is the pure *S*-enantiomer, and bupivacaine is the racemic mixture of the *R*- and *S*-enantiomers, ropivacaine should have greater anesthetic potency (i.e., a lower concentration of ropivacaine might have the anesthetic potency of a higher concentration of bupivacaine). A small, open, pilot study undertaken by two of the authors in a small

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group of five patients undergoing upper extremity surgery indicated that 0.25% ropivacaine provided excellent surgical anesthesia in all five patients.

The purpose of the present study is to expand on that pilot study and to compare the anesthetic characteristics of this concentration of ropivacaine with those of 0.25% bupivacaine when used for brachial plexus block using the subclavian perivascular approach.

Methods

This study was designed as a randomized, double-blind, parallel-group clinical trial. The institutional review boards at both institutions provided approval before initiation of the study, and all patients gave informed consent before being included. The 44 patients selected for inclusion were ASA physical status I and II and were scheduled to undergo elective surgery on the upper extremity under brachial plexus block anesthesia. Excluded from the study were patients with a history of allergy to amide local anesthetics and women who were pregnant.

The patients were randomly assigned to two equal groups on the basis of the local anesthetic to be utilized, so that 22 patients received 0.25% ropivacaine without epinephrine and 22 patients received 0.25% bupivacaine, also without epinephrine. The same protocol was followed at each institution. All of the patients were unpremedicated until they arrived in the operating room, at which time midazolam was titrated intravenously to a maximum of 3.0 mg to relieve anxiety before administration of the block. Each patient then received a subclavian perivascular block according to the technique previously described by Winnie (8). After a paresthesia radiating to a point below the shoulder had been elicited and aspiration for blood was negative, 3 mL of the study drug was injected rapidly to produce a "pressure paresthesia" to confirm proper placement of the needle. The remaining 37 mL was then injected over a period of approximately 1 min, with aspiration repeated every 5 mL. The intercostobrachial and medial brachial cutaneous nerves were then blocked separately by a subcutaneous injection of 5 mL of the study drug superficial to the axillary artery. In any given case, if after the injection of the study drug there was inadequate analgesia for the surgical procedure, appropriate supplemental nerve blocks were performed or general anesthesia was induced. Whenever supplementary nerve blocks were required, data were included only from those dermatomes that exhibited blockade before the supplemental blocks.

Evaluation of sensory and motor function was performed before the administration of the block and then at 2, 5, 10, 15, 20, 25, and 30 min after the block. For the next 5 h, sensory and motor function were evaluated every 15 min, for the subsequent 7 h every 30 min, and then every 60 min until recovery was complete. Sensory function was assessed in the C-2 through T-2 dermatomes and graded such that no loss of sensation to pinprick was scored as 0, analgesia (patient feels touch but not pinprick) was scored as 1, and anesthesia (patient does not even feel touch) was scored as 2. Motor block was assessed at the shoulder by asking the patient to elevate the arm while keeping the elbow straight to evaluate the degree of blockade of the superior trunk and at the hand by determining the strength of handgrip to evaluate the degree of blockade of the middle and inferior trunks. Motor function was graded such that no weakness was scored as 0, paresis was scored as 1, and paralysis was scored as 2.

Table 1. Clinical Characteristics of 44 Patients Undergoing Upper Extremity Surgery

Study group	Age (yr)	Height (cm)	Weight (kg)	Gender (M/F)
Ropivacaine 0.25%	43 ± 15	173 ± 11	78 ± 20	19/3
Bupivacaine 0.25%	44 ± 14	174 ± 9	79 ± 17	19/3

M, male; F, female.
Mean ± SD.

In addition to sensory and motor function, heart rate and arterial blood pressure were monitored and recorded before premedication; before administration of the block; 2, 5, 10, 15, 20, 25, 30, 45, and 60 min after the block; and then every 30 min for an additional 2 h. Any signs or symptoms of central nervous system toxicity or any other adverse experiences were also recorded.

For statistical analysis of the data, continuous variables such as onset and duration of analgesia, anesthesia, paresis, and paralysis were tested using a Wilcoxon rank sum test. Binary variables, such as the presence or absence of sensory or motor block, were analyzed with the χ^2 test or Fisher's exact test. A P value of ≤0.05 was considered to represent statistical significance.

Results

There was no significant difference between the two groups of patients in terms of age, height, weight, or male/female ratio (Table 1). The frequency of analgesia in the C-2 through T-2 dermatomes did not significantly differ between the 0.25% ropivacaine and 0.25% bupivacaine groups: 76% or more of the patients in both groups developed analgesia in the C-5 through T-1 dermatomes of the brachial plexus, whereas few patients developed analgesia in the C-2

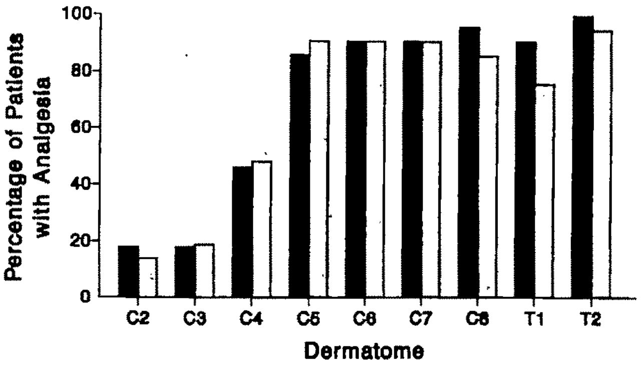

Figure 1. The frequency of analgesia was 76% or greater in the C-5–T-1 brachial plexus dermatomes and did not differ significantly between the 0.25% ropivacaine (■) and 0.25% bupivacaine (▨) groups. Few patients developed cervical plexus (C-2–C-4) analgesia.

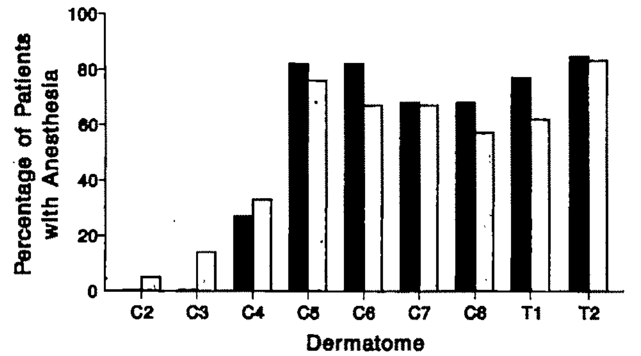

Figure 2. The frequency of anesthesia in the C-5–T-1 brachial plexus dermatomes ranged from 57% to 82% and did not differ significantly between the 0.25% ropivacaine (■) and 0.25% bupivacaine (▨) groups. Anesthesia developed infrequently in the cervical plexus (C-2–C-4).

through C-4 dermatomes of the cervical plexus (Figure 1). There was no significant difference between the two groups with respect to the frequency of anesthesia in the C2 through T-2 dermatomes: 57%–82% of the patients in both groups developed anesthesia in the C-5 through T-1 dermatomes of the brachial plexus, and again, only a small percent of patients developed anesthesia in the C-2 through C-4 dermatomes of the cervical plexus (Figure 2).

The onset times for analgesia and anesthesia also did not differ significantly between the ropivacaine and bupivacaine groups (Table 2). The mean onset time for analgesia ranged from 12.0 to 19.7 min for ropivacaine and 11.2 to 20.2 min for bupivacaine, whereas the mean onset time for anesthesia ranged from 23.7 to 48.2 min for ropivacaine and 23.3 to 47.1 min for bupivacaine. The duration of analgesia and anesthesia also did not differ significantly between the two groups, with a mean duration of analgesia ranging from 9.2 to 13.0 h and a mean duration of anesthesia ranging from 5.0 to 10.2 h (Table 3).

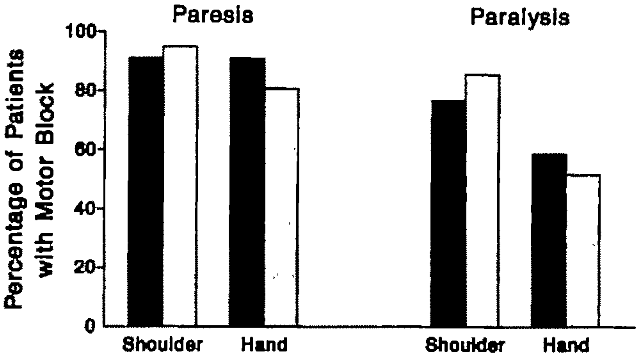

Figure 3. There was no significant difference between the 0.25% ropivacaine (■) and 0.25% bupivacaine (▨) groups in the frequency of motor block of any degree (paresis/paralysis of the hand and shoulder). Although motor paresis of the shoulder and hand was frequent (>80% of patients), paralysis of the hand was less common (52%–59% of patients).

Paresis of the shoulder and hand muscles developed in >80% of patients in both groups, whereas complete paralysis was less frequent (Figure 3). There was no significant difference between groups in the frequency of paresis or paralysis of either the shoulder or hand (Figure 3). Similarly, the onset and duration of motor block did not differ between groups (Table 4) except for the onset of paresis in the hand, which was significantly faster in the bupivacaine group.

Nine patients in the bupivacaine group and eight patients in the ropivacaine group required supplemental blocks or general anesthesia. The specific types of supplemental blocks used are listed in Table 5. One patient in the bupivacaine group was excluded from the analysis of efficacy because of a deviation from the protocol. Three patients in each group had Horner's syndrome, and one patient in each group experienced tourniquet pain. There were no significant differences between the two groups with respect to changes in systolic or diastolic blood pressure, heart rate, mean arterial pressure, or rate-pressure product at any time during the study.

Discussion

The efficacy of 0.25% ropivacaine for brachial plexus anesthesia was virtually identical to that of 0.25% bupivacaine in terms of onset and duration of sensory block as well as the need for supplementation. However, the 0.25% concentration of both agents appears to be unsuitable for brachial plexus block because of a high failure rate. The supplementation rate of 36% for the ropivacaine group and 43% for the bupivacaine group is in sharp contrast to the supplementation rate

Table 2. Onset of Sensory Block

	Onset of analgesia (min)		Onset of anesthesia (min)	
Level	Ropivacaine 0.25%	Bupivacaine 0.25%	Ropivacaine 0.25%	Bupivacaine 0.25%
C-5	19.2 ± 22.2	11.5 ± 14.0	48.1 ± 43.4	37.8 ± 40.7
C-6	12.0 ± 10.7	20.2 ± 28.7	47.8 ± 51.4	47.1 ± 60.4
C-7	18.6 ± 22.9	14.3 ± 18.7	48.2 ± 42.7	40.7 ± 35.7
C-8	15.1 ± 24.0	11.2 ± 16.4	43.8 ± 44.6	23.3 ± 21.9
T-1	19.7 ± 32.2	11.6 ± 17.4	23.7 ± 21.3	26.5 ± 34.5

Mean ± SD.

Table 3. Duration of Sensory Block

	Duration of analgesia (h)		Duration of anesthesia (h)	
Level	Ropivacaine 0.25%	Bupivacaine 0.25%	Ropivacaine 0.25%	Bupivacaine 0.25%
C-5	10.7 ± 2.6	13.0 ± 4.9	5.0 ± 2.8	8.2 ± 4.7
C-6	10.2 ± 3.5	11.6 ± 3.2	6.0 ± 3.4	8.0 ± 3.0
C-7	9.2 ± 4.2	11.0 ± 4.4	6.7 ± 2.7	8.1 ± 4.1
C-8	9.4 ± 3.5	12.1 ± 5.2	7.3 ± 3.2	10.2 ± 3.8
T-1	9.8 ± 2.5	12.2 ± 4.4	7.7 ± 2.2	9.2 ± 3.9

Mean ± SD.

Table 4. Onset and Duration of Motor Block (min)

	Onset of motor block (min)		Duration of motor block (h)	
	Ropivacaine 0.25%	Bupivacaine 0.25%	Ropivacaine 0.25%	Bupivacaine 0.25%
Hand				
Paresis	29.0 ± 41.0[a]	7.1 ± 6.4[a]	9.4 ± 3.6	12.1 ± 4.2
Paralysis	41.7 ± 45.8	27.0 ± 35.2	8.0 ± 3.0	9.8 ± 4.9
Shoulder				
Paresis	9.1 ± 16.5	5.3 ± 5.3	10.8 ± 2.7	13.6 ± 5.4
Paralysis	12.2 ± 8.3	14.8 ± 13.4	8.6 ± 1.8	11.4 ± 5.6

Mean ± SD.
[a] $P < 0.05$.

of 8% for both local anesthetics when used in a 0.5% concentration (2) observed in a previous study. The high rate of supplementation noted for the 0.25% concentrations appears to be due to the fact that this concentration is borderline with respect to the threshold necessary to develop anesthesia; for, although the incidence of analgesia in the C-5 through T-1 dermatomes ranged from 76% to 96%, the incidence of anesthesia in these dermatomes was much less. Likewise, although motor paresis at the shoulder and hand frequently developed (in >80% of all patients), complete motor paralysis was frequently not seen (in the hand 59% and 52%, respectively, for ropivacaine and bupivacaine).

The main advantage of ropivacaine over bupivacaine is its lesser potential for cardiac toxicity. In isolated rabbit Purkinje fiber ventricular muscle preparations, Moller and Covino (9) demonstrated that the effect of ropivacaine on altering various electrophysiologic variables was greater than lidocaine but less than bupivacaine. Feldman et al. (7) demonstrated in a dog model that although the convulsive doses of ropivacaine and bupivacaine were similar, ropivacaine was less arrhythmogenic than bupivacaine. Other animal studies have confirmed the lower cardiac toxicity of ropivacaine compared with bupivacaine (6,10,11). The one human study that has examined the acute toxicity of ropivacaine was reported by Scott et al. (12) in a group of 12 volunteers who received intravenous infusions of ropivacaine and bupivacaine up to a maximal dose of 150 mg. It was noted that ropivacaine caused less central nervous system symptoms and could be tolerated at a larger total dosage than bupivacaine (12). In addition, electrocardiogram and echocardiogram evidence of depression of conductivity and contractility appeared at smaller dosage and lower plasma concentrations with bupivacaine than with ropivacaine (12). In our study, we noted no overt signs of cardiac or central nervous system toxicity with either bupivacaine

Table 5. Number of Patients Requiring Supplementation of Anesthesia and Analgesia

	Ropivacaine 0.25%	Bupivacaine 0.25%
Total no. of patients requiring supplementation	8	9
General anesthesia	4	4
Nerve blocks		
Axillary block	1	
Radial nerve	1	1
Median nerve	3	2
Ulnar nerve	4	4
Medial antebrachial cutaneous nerve		1
Local infiltration		1

(0.89–2.0 mg/kg) or ropivacaine (0.81–2.3 mg/kg). In the two previous brachial plexus studies reported with slightly higher doses (up to 3.2 mg/kg of bupivacaine and 3.1 mg/kg of ropivacaine), there was also no evidence of toxicity. It should be noted, however, that in each of these studies, the patients were premedicated with midazolam, which could increase the threshold, at least for central nervous system toxicity. In addition, unlike the volunteers studied by Scott et al. (12), our patients did not undergo formal electrocardiogram analysis or echocardiographic studies to determine more subtle signs of cardiac toxicity.

In conclusion, we have demonstrated that for subclavian perivascular brachial plexus block, despite theoretical potency of ropivacaine because of exclusion of the less potent *d*-isomer, 0.25% ropivacaine is similar in quality to 0.25% bupivacaine in most aspects. Both local anesthetics, however, are frequently associated with inadequate sensory or motor block, or both. In view of the high rate of supplementation necessary with both 0.25% ropivacaine and 0.25% bupivacaine, we recommend using the 0.5% concentration of these local anesthetics to provide brachial plexus anesthesia.

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Epidural Clonidine Enhances Postoperative Analgesia From a Combined Low-Dose Epidural Bupivacaine and Morphine Regimen

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In a randomized, double-blind, placebo-controlled trial, the value of adding clonidine to a low-dose epidural regimen for postoperative pain treatment was assessed. Twenty-four patients scheduled for hysterectomy during combined thoracic epidural (bupivacaine and morphine) and general anesthesia were studied. Postoperative analgesia consisted of epidural bupivacaine (5 mg/h) and morphine (0.1 mg/h) for 12 h. In addition, the patients randomly received clonidine (75 μg), followed by an infusion of 18.75 μg/h or saline solution (placebo) epidurally. Pain was evaluated at rest, during cough, and during mobilization every hour. Sensory level of analgesia was evaluated by pinprick. We found no significant difference in pain scores at rest between the clonidine and placebo groups but an enhanced analgesic effect by clonidine during cough and mobilization ($P < 0.05$). Arterial blood pressure decreased significantly during clonidine infusion and remained lower than in the control group throughout the study. We conclude that a continuous low-dose epidural clonidine infusion enhances analgesia from a combined low-dose epidural bupivacaine and morphine regimen after hysterectomy; however, the concomitant decrease in arterial blood pressure during epidural clonidine deserves further study before such a regimen can be recommended.

(Anesth Analg 1992;75:607–10)

Despite developments in the treatment of postoperative pain, many patients still have pain after surgery (1). The explanation hereto may be lack of an effective postoperative pain treatment regimen without side effects. We have previously advocated the principle of multimodal pain therapy ("balanced analgesia") based on the hypothesis that a combination of analgesics with different sites of action may improve overall pain relief (2). Epidural administration of combined local anesthetics and opioids may provide improved pain relief but still carries the risk of side effects when doses approach levels necessary for total pain relief (3–8). Clonidine, an α_2-adrenergic agonist, reduces but does not eliminate pain after surgery (9–12). The mechanism of pain relief seems to be different from that of opioids, because it can be antagonized by phentolamine but not naloxone (13). However, with the relatively high doses of clonidine used in clinical investigations, significant hemodynamic depression with hypotension was observed (9–12).

The aim of this study was to evaluate the effect of adding low-dose clonidine to a very low-dose regimen of continuous epidural local anesthetics and morphine on pain relief and arterial blood pressure after hysterectomy.

Methods

A randomized, placebo-controlled, double-blind trial was designed in agreement with the Helsinki II Declaration. The study was approved by the regional ethical committee and the Danish Health Service, and informed consent was obtained from each patient.

Twenty-four patients scheduled for abdominal hysterectomy were premedicated with diazepam (0.2 mg/kg). Before induction of general anesthesia, a 20-gauge epidural catheter was inserted between T-10 and T-11 and 3 mL of plain (0.5%) bupivacaine as a test dose, followed by 5 mL of plain (0.5%) bupivacaine plus 1 mg of morphine (2.5 mL of 0.4 mg/mL) was used to produce epidural analgesia. General anesthesia was induced with thiopental (3–5 mg/kg

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IV). After pancuronium (0.01 mg/kg IV), succinylcholine (1.5 mg/kg) was used to facilitate orotracheal intubation. General anesthesia was maintained with N_2O/O_2 (2:1) and isoflurane (0.5%–1.5%).

Postoperative pain treatment consisted of epidural 0.125% bupivacaine (4 mL/h) and morphine (0.1 mg/h) initiated 30 min after the initial dose of bupivacaine and morphine had been administered and scheduled for 12 h, delivered by a Pharmacia Deltec infusion pump. The patients were randomized to receive in a double-blind fashion either clonidine (75 μg) dissolved in 3 mL of saline solution immediately after the initial dose of bupivacaine and morphine, followed by 18.75 μg/h together with the infusion of bupivacaine and morphine for 12 h (group I) or saline solution (group II). The volume of the epidural infusion was 4 mL/h in both groups. On request, the patients received supplemental morphine (0.15 mg/kg) intramuscularly.

Pain was evaluated by one of the authors every 2 h at rest, during cough, and during mobilization from the supine to the sitting position in bed by a 10-cm visual analogue scale and verbal rate scoring (0 = no pain, 1 = slight pain, 2 = moderate pain, 3 = severe pain, and 4 = unbearable pain). Sensory level of analgesia was evaluated by pinprick. Blood pressure was measured every hour. Ephedrine was administered if systolic arterial blood pressure decreased to below 80 mm Hg.

Results are expressed as median values and ranges. A Mann-Whitney test for unpaired data was used to compare the two groups. Because the trial design implied multiple intraperson assessments of pain over time, the relevant statistical method was analysis of variance. Because of ordinal measurements, we used the corresponding nonparametric method in which treatments were compared with the Mann-Whitney test for unpaired data disregarding time, and both the factor time and the interaction between time and treatment were assessed by Friedman's test; $P < 0.05$ was considered significant (14).

Results

Two patients, one from each group, were excluded from the study because of displacement of the epidural catheter, and the study thus comprised 22 patients. There were no differences in demographic data between the two groups (Table 1). Median visual analogue scale and verbal rate scores at rest, during cough, and during mobilization are shown in Figure 1. There was no significant difference between groups I and II at rest, in contrast to significantly higher pain scores during cough and mobilization in the saline solution group ($P < 0.05$). The supplemental intramuscular doses of morphine in groups I and II were, respectively, 0 mg (0–10) and 0 mg (0–20) [median (range)]; $P > 0.05$.

Table 1. Demographic Data of Patients Undergoing Abdominal Hysterectomy

	Epidural + clonidine group (n = 11)	Epidural + placebo group (n = 11)
Age (yr)	46 (34–52)	47 (35–65)
Weight (kg)	57 (53–80)	60 (54–75)
Height (cm)	167 (157–180)	167 (159–173)
Duration of surgery (min)	120 (70–180)	105 (55–150)

Median (range); P = NS.

The frequency of patients with no pain (verbal rate score = 0) experienced during cough during the 12-h period in group I was 45% compared with 9% in group II; the median difference between groups was 36% (95% confidence interval 2%–70%).

No decrease in sensory level of analgesia was seen during the 12-h period, and there was no difference between the groups ($P > 0.05$) (Figure 2). There was a significant decrease in arterial blood pressure in the clonidine-treated patients (group I) compared with the initial value ($P < 0.05$) (Figure 3). The amount of supplemental ephedrine during surgery was 10 mg (0–50) in group I and 0 mg (0–50) in group II; after surgery, 0 mg (0–25) in group I and 0 mg (0–10) in group II; and totally, 10 mg (0–50) in group I and 0 mg (0–50) mg in group II [median (range)]; $P > 0.05$. No respiratory complications indicating treatment were seen.

Discussion

The use of epidural local anesthetics in combination with morphine is one of the most powerful methods to produce postoperative pain relief. However, there is significant risk for serious side effects, such as respiratory depression, hypotension, and urinary retention, when doses necessary to produce total pain relief are used (7,8). When the doses of morphine and local anesthetics are reduced, the number of side effects may decrease but at the risk of inadequate pain relief (5,6). Therefore, there is a need for new approaches to the treatment of severe, acute pain. We have previously advocated the term "balanced analgesia" (i.e., a combination of low doses of different drugs having different antinociceptive characteristics) (2,15), with the goal of increasing pain relief and reducing the side effects.

The α_2-agonists, like clonidine, probably activate postsynaptic receptors at noradrenergic pathways involved in endogenous pain control (16), both in

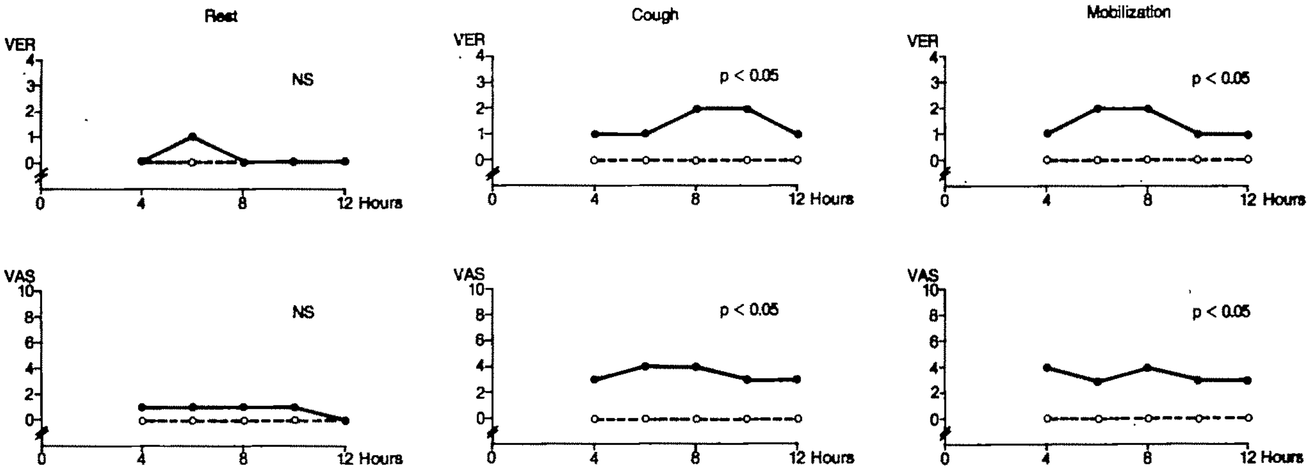

Figure 1. Median postoperative pain scores during rest (*left*), cough (*middle*), and mobilization (*right*) during continuous epidural bupivacaine (5 mg/h) and morphine (0.1 mg/h) plus epidural clonidine (18.75 $\mu g/h$) (—O—) ($n = 11$) or placebo (—●—) ($n = 11$) after hysterectomy. Significant difference ($P < 0.05$) at cough and mobilization. VER, verbal rate score; VAS, visual analogue scale.

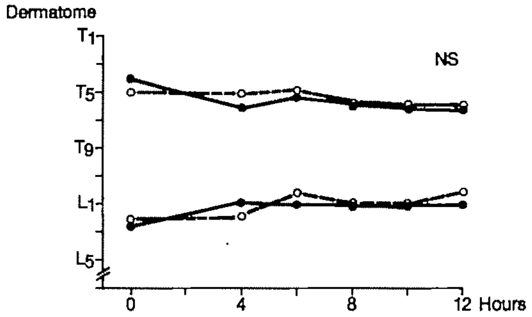

Figure 2. Median sensory level of analgesia (pinprick) during continuous epidural bupivacaine (5 mg/h) and morphine (0.1 mg/h) plus epidural clonidine (18.75 $\mu g/h$) (—O—) ($n = 11$) or placebo (—●—) ($n = 11$) after hysterectomy ($P > 0.05$).

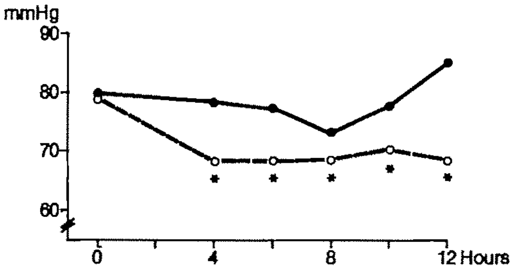

Figure 3. Median arterial blood pressure during continuous epidural bupivacaine (5 mg/h) and morphine (0.1 mg/h) plus epidural clonidine (18.75 $\mu g/h$) (—O—) ($n = 11$) or placebo (—●—) ($n = 11$) after hysterectomy. $^*P < 0.05$ compared with initial value; $P < 0.05$ between the treatments.

the dorsal horn of the spinal cord (17) and at the supraspinal level (18). This effect is different from both opioids and local anesthetics. The difference in analgesic effect of clonidine after intramuscular or epidural administration may be none or small (12).

Clonidine has been shown in most (9–12), but not all (19), studies to have beneficial effects on postoperative pain. Because clonidine in experimental studies may have very low neural toxicity after intrathecal administration (20), we added a low dose of clonidine to a very low-dose continuous epidural local anesthetic and morphine regimen to improve pain relief.

Our results demonstrate that epidural clonidine (75 μg) followed by an infusion of 18.75 $\mu g/h$ enhances postoperative analgesia of a very low-dose epidural bupivacaine and morphine regimen. These results are in accordance with the results from experimental studies in which a synergistic or additive analgesic effect of α_2-agonists and morphine (21,22) has been demonstrated. A synergistic/additive analgesic effect has also been demonstrated with the combination of local anesthetics and clonidine (23,24).

In most studies, clonidine has been administered by a bolus dose injection, resulting in analgesia lasting from 2 to 5 h (9,10,12). The short duration of the drug makes continuous infusion more suitable for postoperative pain relief compared with bolus injection. A continuous infusion may also result in lower peak concentrations in plasma and cerebrospinal fluid, thereby possibly reducing side effects. However, even with our relatively small dose of clonidine, we found a decrease in arterial blood pressure comparable to that observed in studies in which bolus injections were used (9,10,22). Therefore, further studies are needed to evaluate the optimal dose regimen of clonidine with regard to pain relief versus hemodynamic side effects.

In conclusion, we found an increase in analgesia at cough and mobilization when clonidine was added to a continuous low-dose epidural infusion of bupivacaine and morphine. However, the concomitant decrease in arterial blood pressure calls for further studies before such a regimen can be recommended for daily clinical practice.

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Lidocaine and Bupivacaine Cardiorespiratory Toxicity Is Additive: A Study in Rats

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The purpose of this study was to determine whether equipotent solutions of lidocaine, bupivacaine, or a mixture of these compounds infused at a fixed rate in anesthetized rats resulted in equivalent lethal cardiorespiratory toxicity and to establish whether the lethality of the individual drugs was additive. This was assessed by comparing the time to respiratory and circulatory arrest, determining the lethal doses of administered local anesthetic in each group, and ascertaining the concentration of lidocaine or bupivacaine, or both, at the time of circulatory arrest. The times to respiratory and circulatory arrest were similar in rats receiving either lidocaine (2%) or bupivacaine (0.5%) or a mixture of 1% lidocaine and 0.25% bupivacaine. The mean lidocaine-to-bupivacaine cumulative lethal dose ratio (3.36) and concentration ratio (2.33) were determined and used to calculate lidocaine equivalent values for bupivacaine data. Lidocaine equivalent cumulative lethal doses and plasma concentrations were similar in all three groups studied. This work suggests that the lethal cardiorespiratory toxicity of lidocaine and bupivacaine associated with intravenous infusion is additively toxic in rats.

(Anesth Analg 1992;75:611–4)

Different local anesthetics are often combined with advantage in clinical practice (1). The combined toxicity of local anesthetic (LA) mixtures has been investigated in animal studies with conflicting results; synergistic toxicity (2), additive toxicity (3), as well as antagonism of toxicity at higher doses (4), have all been found. Lidocaine and bupivacaine mixtures after subcutaneous administration have been studied in mice and were found to be essentially additive in toxicity and marginally less toxic than the individual compounds (5).

Our purpose was to determine whether a mixture of bupivacaine and lidocaine was also additively toxic when administered intravenously, the preferred method for assessing LA toxicity (6). In addition to assessing this by determining the time to respiratory and circulatory arrest on infusion of the individual compounds as well as the mixture, we wanted to determine whether the lethal doses and lethal plasma concentrations of these drugs were also additive.

Methods

Seventy-one male Long-Evans rats weighing app
imately 360 g were studied with institutional
proval and anesthetized with intraperitoneal pe
barbital (60 mg/kg). Cutdowns were performed i
groin to place right femoral artery and left fe
vein catheters, each 10 cm in length (19 gauge B
cath, Sheffield, England). The arterial catheter
used to measure arterial blood pressure continuo
and display the arterial waveform by means o
oscilloscope set on a scale of 0–300 mm Hg,
a sweep speed of 25 mm/s while the heart
and rhythm were continuously monitored wit
electrocardiogram (ECG). The venous catheter
connected to a calibrated infusion pump for
ministration of the test solution at a rat
0.16 $\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$. Eleven animals received s
solution (group S), and 60 animals were rand
allocated to receive commercially available lidoc
hydrochloride (2%) at 3.2 $\text{mg}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ (grou
bupivacaine hydrochloride (0.5%) at 0.8 mg·k
min^{-1} (group B), or a mixture of lidocaine (
at 1.6 $\text{mg}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ and bupivacaine (0.25%
0.4 $\text{mg}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ (group BL). The investigator
unaware of the LAs administered. All experim
were performed between 8 AM and 1 PM to a

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Table 1. Study Group Characteristics at Baseline in Rats

	Group S	Group L	Group B	Group BL
Weight (g)	367 (6)	364 (4)	359 (4)	354 (5)
Anesthetic time (min)	36.7 (0.6)	38.0 (0.8)	37.9 (1.0)	37.7 (1.3)
Mean arterial pressure (mm Hg)	104 (2)	96 (5)	93 (5)	93 (4)
Respiratory rate (breaths/min)	83 (3)	80 (4)	73 (3)	80 (5)
pHa	7.36 (0.01)	7.36 (0.01)	7.36 (0.01)	7.36 (0.01)
Pa_{O_2} (mm Hg)	100 (2)	99 (4)	99 (4)	96 (2)
Pa_{CO_2} (mm Hg)	39 (1)	39 (1)	39 (1)	38 (1)
Base excess (mEq/L)	−2.6 (0.9)	−2.9 (0.6)	−2.3 (0.4)	−2.8 (0.6)

Mean (±SE) baseline weights, duration of anesthesia before start of experiments (anesthetic time), mean arterial pressure, respiratory rate, and arterial blood gas data for rats that received saline solution (group S, $n = 11$); 2% lidocaine (group L, $n = 20$); 0.5% bupivacaine (group B, $n = 22$); and 1% lidocaine and 0.25% bupivacaine (group BL, $n = 18$); P = NS.

diurnal variations, and the rats were neither oxygenated nor ventilated.

Approximately 35 min after the start of the anesthetic, the time was noted, and baseline measurements of respiratory rate and mean arterial pressure were performed; 0.4 mL of blood was drawn for arterial blood gas analysis. The test solution was then infused from time zero, and the time to cessation of visible respiratory excursion (respiratory arrest) as well as circulatory arrest, defined as an absence of arterial pulsation on the oscilloscope for one screen width, was noted. At this time, the cardiac rhythm on the ECG was noted, the infusion terminated, and a blood sample obtained by direct cardiac puncture for the determination of plasma lidocaine or bupivacaine concentrations, or both. This was determined in triplicate by means of gas chromatography with a method adapted from Tucker (7). The deviation from the expected value ($n = 9$) was 9.6% for bupivacaine and 8.6% for lidocaine over the range 10–50 μg/mL.

Data were analyzed with one-way analysis of variance and the Tukey multiple-range test to determine differences among the groups. A P value of <0.05 was regarded as significant. Results are presented as mean (±SEM).

Table 2. Time to Respiratory and Circulatory Arrest

	Group S	Group L	Group B	Group BL
Respiratory arrest (min)	—	11.6 (0.7)	14.4 (1.4)	14.0 (1.4)
Circulatory arrest (min)	—	12.9 (0.6)	15.6 (1.5)	15.1 (1.4)
Respiratory to circulatory arrest (min)	—	1.35 (0.1)	1.1 (0.1)	1.1 (0.1)

Mean (±SE) times to respiratory and circulatory arrest for rats that received 2% lidocaine (group L, $n = 20$); 0.5% bupivacaine (group B, $n = 22$); and 1% lidocaine and 0.25% bupivacaine (group BL, $n = 18$); P = NS.

Table 3. Cumulative Dose of Local Anesthetic at Time of Circulatory Arrest

	Group L	Group B	Group BL
Lidocaine (mg/kg)	41.3 (2.1)	—	24.2 (2.2)
Bupivacaine (mg/kg)	—	12.3 (1.1)	6.1 (0.6)
Lidocaine equivalent (mg/kg)[a]	41.3 (2.1)	41.3 (3.8)	44.6 (4.1)

Mean (±SE) local anesthetic and lidocaine equivalent cumulative doses at time of circulatory arrest for rats that received 2% lidocaine (group L, $n = 20$); 0.5% bupivacaine (group B, $n = 22$); and 1% lidocaine and 0.25% bupivacaine (group BL, $n = 18$).

[a] Lidocaine equivalent doses calculated from a lidocaine/bupivacaine lethal dose ratio of 3.36 (see text). Lidocaine equivalent dose in group BL not significantly different from groups B and L.

Results

The four groups of rats were studied at equivalent times after the administration of anesthesia and were similar in weight and had similar mean arterial pressures, respiratory rates, and acid-base status at baseline before the administration of the test solution (Table 1). No control animal infused with saline solution died as a result of the methodology used. The times to respiratory and circulatory arrest were similar in the rats receiving lidocaine, bupivacaine, or a mixture containing half the amount of the individual compounds (Table 2) at standard infusion rates. The ECG monitoring revealed that after respiratory arrest, a supraventricular or ventricular tachycardia usually occurred, accompanied by a rapid decrease in arterial blood pressure. Circulatory arrest occurred ±1 min later (Table 2) and was accompanied by a broad complex agonal rhythm on ECG.

Table 3 shows the cumulative doses of lidocaine and bupivacaine at circulatory arrest. By using the mean data for lidocaine and bupivacaine administered separately, the lidocaine/bupivacaine cumulative dose ratio at the time of circulatory arrest could be determined (3,5) and was found to be 3.36. To facilitate the interpretation of results with mixtures, the lidocaine equivalent dose of bupivacaine at circulatory arrest (5) for each individual experiment could thus be calculated by using this factor.

The same methodology was also used to determine lidocaine equivalent plasma concentrations (Ta-

Table 4. Plasma Local Anesthetic Concentration at Time of Circulatory Arrest

	Group L	Group B	Group BL
Lidocaine (μg/mL)	289.1 (31.5)	—	134.9 (14.0)
Bupivacaine (μg/mL)	—	123.9 (9.3)	88.4 (6.6)
Lidocaine equivalent (μg/mL)[a]	289.1 (31.5)	288.6 (21.4)	338.2 (23.2)

Mean (±SE) local anesthetic and lidocaine equivalent concentrations at time of circulatory arrest for rats that received 2% lidocaine (group L, n = 20); 0.5% bupivacaine (group B, n = 22); and 1% lidocaine and 0.25% bupivacaine (group BL, n = 18).

[a] Lidocaine equivalent concentrations calculated from a lidocaine/bupivacaine lethal dose ratio of 2.33 (see text). Lidocaine equivalent concentrations not significantly different between group BL and groups B and L.

ble 4). Lidocaine equivalent cumulative doses (Table 3) and plasma concentrations (Table 4) at time of circulatory arrest were similar when data for either of the individual compounds were compared with those for the lidocaine and bupivacaine mixture.

Discussion

This study in rats indicates that with regard to lethal cardiorespiratory depression, an equipotent mixture of lidocaine and bupivacaine is no more toxic than the individual compounds. The times to respiratory and circulatory arrest were similar in the three groups studied, as were the cumulative lethal doses and concentrations expressed in lidocaine equivalent values.

This study was designed to assess the effect of intravenous injection of clinically used concentrations of LAs administered individually or as a mixture in rats that were neither oxygenated nor ventilated to mimic the inadvertent intravenous injection or very rapid absorption of LAs in the clinical situation.

The purpose of this study, however, was not to establish individual organ system toxicities (i.e., central nervous system, respiratory, or cardiovascular toxicity for LAs) nor to investigate the mechanism of death, but rather to determine whether LAs administered intravenously individually or as a mixture had the same lethal potential. We took as the endpoint for this investigation the time to circulatory arrest rather than electrical asystole, because this would have resulted in falsely elevated values for the lethal LA concentrations, owing to the absence of hepatic blood-flow-dependent metabolism of continuously infused drug.

Death was most likely precipitated by respiratory arrest, and circulatory arrest was probably due to a combination of hypoxia, acidosis, and LA toxicity. Because an agonal rhythm persisted on ECG monitoring in the absence of a detectable arterial pressure waveform, the terminal event was probably acute cardiac failure rather than cardiac standstill. Convulsions that are a common feature of LA toxicity (3,5) were witnessed in only a single rat from group B. The lack of this toxic manifestation in our experiments can probably be attributed to the use of pentobarbital for anesthesia.

Lidocaine (2%) and bupivacaine (0.5%) were separately infused at equipotent (8) concentrations that were also in proportion to their lethal dose ratio in mice (8) and dogs (9). This proportion was maintained when these concentrations of LAs were mixed, thus achieving a final equipotent concentration of lidocaine (1%) and bupivacaine (0.25%) in the administered mixture. This methodology was adopted so that standard volumes of solution (0.16 mL/kg) were infused in all groups.

Intravenous administration is the most suitable route for assessing the toxicity of LAs, because it avoids the influence of various kinetic factors (e.g., drug permeability through tissue-blood barriers) (6). The toxicity of an LA depends on the plasma concentration but more specifically on the free fraction (10). During continuous infusion of an LA at a fixed rate, the plasma concentration depends on the rate of metabolism, and because lidocaine is more rapidly metabolized than bupivacaine in humans (11), the combination of these drugs may be less toxic than an equipotent infusion of bupivacaine. On the other hand, McNamara et al. (12) showed an increase in the free fraction of lidocaine in the presence of bupivacaine at clinical concentrations in vitro, which suggests that the combined administration of these drugs might be more toxic. The similar times for respiratory and circulatory arrest in the three groups studied (Table 2) suggest that the effect on LA toxicity of the previously mentioned two opposing kinetic factors may have balanced out when the two LAs were administered as a mixture.

The cumulative lethal dose ratio for lidocaine to bupivacaine of 3.36 determined in this study was less than the proportion of these drugs in the infused anesthetic mixture, which was based on a lethal dose ratio of 4:1 established in mice (8) and dogs (9). This is probably reflected in the nonsignificant tendency for earlier cardiorespiratory arrest in group L (Table 2).

This study allowed a comparison of the toxic concentrations at the time of circulatory arrest and is the first study to assess this for a mixture of lidocaine and bupivacaine. There was no statistical difference in the lidocaine equivalent concentrations at the time of circulatory arrest in those rats receiving the mixture compared with those receiving the individual drugs, suggesting that, independent of kinetic factors, lidocaine and bupivacaine are additively toxic (Table 4).

It is noteworthy that the cumulative lethal dose ratio (3.36) was significantly more than the lethal plasma concentration ratio of 2.33 ($P = 0.01$). This difference is probably due to pharmacokinetic differences, such as the more rapid elimination of lidocaine with respect to bupivacaine, as discussed earlier.

The limited number of investigations into the combined toxicity of LAs administered as mixtures were not directly comparable with the present study, because these investigated different LA mixtures in mice (2,4), rats (13), and monkeys (3). The only other study (5) that investigated the use of lidocaine and bupivacaine combined studied this in mice after subcutaneous administration of solutions mixed in proportion to their convulsive concentration. These authors concluded that this mixture was no more toxic than the individual drugs.

In conclusion, our work in rats suggests that the lethal cardiorespiratory toxicity of lidocaine and bupivacaine associated with intravenous infusion is additive.

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Noninvasive Percutaneous Induction of Topical Analgesia by a New Type of Drug Carrier, and Prolongation of Local Pain Insensitivity by Anesthetic Liposomes

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We studied the duration of action and permeability of common analgesics and local anesthetics applied dermally via new carriers—transfersomes—in rats and humans. The therapeutic potential of analgesic transfersomes was evaluated in Sprague-Dawley rats subjected to heat and pressure stimuli. Results were compared with those obtained from administration of lidocaine-containing standard liposomes. In rats, subcutaneous injections of 2% lidocaine solution and of liposomal or transfersomal suspension resulted in a strong initial analgesic effect that decayed within 6–7 min. Characteristic withdrawal time is approximately 30 s. Dermally applied analgesic transfersomes, by contrast, increased heat stimulus reaction to >70 s, 130% longer than in controls that received a placebo or a standard aqueous lidocaine solution. In humans, we tested two groups of nine male and female volunteers, aged between 25 and 60 yr, for pain-suppressing activity assessed by the pinprick method. Each subject received a total of 0.5 mL of a transfersomal preparation containing 7% lidocaine or 4% tetracaine over a forearm area of 9 cm. We conclude that the effectiveness of dermally applied anesthetic transfersomes is similar to that of the corresponding subcutaneous injections of similar drug quantities and that optimally designed transfersomes offer a suitable and promising means for the noninvasive treatment of local pain with direct, topical drug application.

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The most popular route for the introduction of analgesics into the body is per os. The effects of oral pain treatment are often relatively diffuse and weak, however. In the case of strong peripheral pain, subcutaneous drug injections are therefore the therapy of choice (1). Analgesic drugs are hardly ever applied percutaneously, owing to the poor therapeutic efficiency of such application resulting from the inadequate penetration of most analgesics through the intact skin.

To date, the development of skin-active analgesic preparations has been based primarily on classical galenic formulations, such as creams or ointments (2–4), which have only a limited transdermal transport potential (5). Only occasionally are more modern drug preparations, such as suspensions of lipid vesicles (liposomes [6]), also used (7). This may be the reason why no analgesic preparation has as yet proved its suitability for dermal application: the resulting analgesia induced by all widely known analgesic formulations is either too weak or sets in too slowly or both. Consequently, even the best current high-potency analgesic formulations for topical use are normally applied under occlusion, the recommended duration of drug application occasionally extending to hours.

We believe that a new type of drug carrier—transfersomes—can circumvent this problem and provide formulations of unprecedented quality for the induction of local anesthesia. We report the first account of such newly developed analgesic transfersomes for the management of local pain in rats and humans. We show that analgesic transfersomes can penetrate rapidly through the intact dermis and can also bring appreciable amounts of analgesic drugs into the skin. Depending on their composition, size, and concentration, the transfersomal drug carriers can reach the cutis as well as the subcutis and, consequently, may affect strongly the physiologic functions of nociceptors and other nerve endings.

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With the use of analgesic transfersomes, peripheral pains can thus be suppressed at their very roots.

Methods

Anesthetic Transfersomes

Transfersomes are specially designed, chiefly vesicular, particles. Each transfersome consists of at least one inner aqueous compartment. This is surrounded by a lipid bilayer with specially tailored properties. In the morphologic but not the functional sense, the transfersomes thus resemble lipid vesicles—so-called liposomes. Transfersomes, as used in this study, typically had a diameter of 0.2 μm, with a standard deviation of approximately 30%.

Transfersomes can be made from many synthetic or natural lipids. To ensure optimal biocompatibility, in this study biologic phospholipids from soybean were used as the basic transfersomal component. Specifically, the most common phospholipid, phosphatidylcholine, was chosen and used as a nearly pure (95%+) compound. In addition to phosphatidylcholine, all present transfersomes also contained a small amount of sodium cholate as well as 3%–7% ethanol (puriss). The relative concentration of sodium cholate varied between 50 and 20 mol%, depending on the details of the experiment. This corresponds to a surfactant/lipid weight ratio of between 24% and 10%.

Owing to the amphiphilicity of all standard local anesthetics, such drugs partition preferentially into the interfacial region between the lipid bilayer interior and the aqueous subphase (8–10). They are thus easy to encapsulate. For example, lidocaine can be incorporated into a typical transfersomal preparation nearly quantitatively, provided that the total lipid concentration is sufficiently high. (It is noteworthy that the presence of the drug also modifies the cholate-phospholipid interactions and affects the colloidal stability of the vesicles.)

The investigated transfersome formulations typically contained 2% lidocaine (as a free base) and 4%–8% lipids (wt/vol). This drug/lipid combination is relatively efficient in terms of its therapeutic efficiency in animals and humans. It is colloidally not very stable, however, probably owing to the surfactantlike properties of the encapsulated drug molecules. Further optimization of the detailed composition of analgesic transfersomes for human therapy, therefore, remains to be carried out.

Local Analgesia Assays

To evaluate the therapeutic potential of analgesic transfersomes in animals, we used two test systems. In the "tail-flick" assay, as introduced by D'Amour and Smith (11), a rat's tail was excited by a medium heat stimulus originating from a beam of light (LI 7100 Letica) directed onto the test region. The mean period of time required for a locally anesthetized rat to withdraw its drug-treated tail from the hot spot was then determined. The difference between the results obtained for the transfersome- or saline-treated rats was taken to be a measure of the degree of local analgesia.

The pressure-sensitive nociceptors on the rat's tails were studied by the Eagle and Carlson assay (12) using a Basile analgesimeter. In brief, the threshold value of the mechanical stress needed for the withdrawal of the rat's tail on the induction of pressure was measured. Typically, the weight imposed on a locally treated rat's tail was gradually increased at a constant rate until the test animal spontaneously withdrew its tail. The pressure at which this occurred was registered as a function of the drug-action time and taken to be proportional to the efficacy of the topical analgesia.

For each experiment, a group of 6–10 (most frequently 7–8) Sprague-Dawley rats was used. All animals had a mean body weight of 150 g, were fed ad libitum, had free access to water, and were kept in individual cages before the experiments. All drugs were applied in a volume of 0.1 mL to an area approximately 1 cm long, roughly 1.2 cm from the root of the tail.

To be able to compare different data sets quantitatively and, in particular, to determine the pharmacokinetic system variables, the following phenomenologic expression was used for the experimental data analysis:

$$\text{Anesthesia}(t) = \kappa_1 \exp[(t - t_d)/\tau_1] + \kappa_2 \exp(t/\tau_2), \quad (1)$$

where τ_1 and τ_2 are two characteristic time constants, and t_d is the delay time of the drug action. (Optimal model variable values are given in the legend to Figure 7.)

All results from animal experiments were checked for significance by Student's *t*-test. Values of $P \leq 0.001$, $P \leq 0.01$, and $P \leq 0.05$ were considered significant.

In the studies in humans (who gave informed consent), two groups of nine male and female volunteers, aged between 25 and 60 yr, were tested for the pain-suppressing activity elicited by the dermally applied analgesic transfersomes. Each subject received a total of 0.5 mL of a transfersomal preparation containing 7% lidocaine or 4% tetracaine on one forearm over an area of 9 cm^2 (these concentrations correspond to the upper drug concentration limit in the present formulations that still maintain short-term stability while also being clinically useful).

The application area was kept under occlusion by a

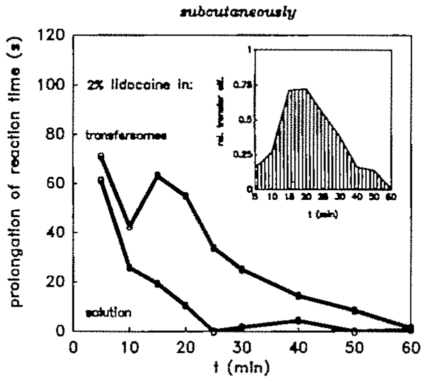

Figure 1. Analgesic action of a subcutaneous injection of 2% lidocaine solution (*lower curve*) or of the corresponding suspensions of liposomes (transfersomes) (*upper curve*), as measured with the rat "tail-flick" assay. The *insert* shows the net effect of drug encapsulation into lipid vesicles. Pain insensitivity resulting from an injection of lidocaine solution lasts only for approximately 10 min; if the same amount of drug is formulated in a liposomal suspension, the resulting analgesia lasts approximately 50 min, reaching 75% of the maximal effect 15–20 min after drug application. All differences but the last differ significantly ($P \leq 0.001$) from the control results. t = time.

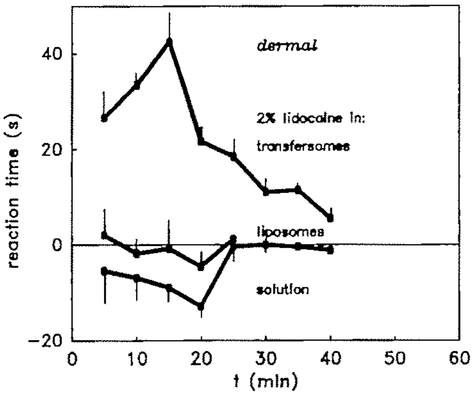

Figure 2. Lag time between induction of a heat stimulus on rat tails and the resulting withdrawal reaction after dermal applications of different analgesic agents. Given values were obtained by subtracting normal reaction times (NaCl treated) from the corresponding drug response data. Animals treated with an aqueous lidocaine solution have a slightly shorter reaction time than animals from the control group treated with 0.9% NaCl. Topically applied analgesic standard liposomes do not reduce the sensitivity of rat tails to pain; conversely, the dermally applied transfersomes induce an appreciable local analgesia within 5 min after application. All results obtained with transfersomes, and no other data points, differ significantly from the controls; $P \leq 0.001$.

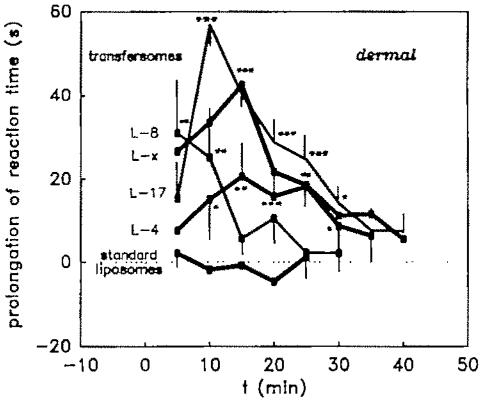

Figure 3. Prolongation of the reaction time to local pain as measured with the "tail-flick" assay with animals given preparations of analgesic transfersomes, liposomes, or analgesic solution directly on the intact skin surface. Lipid concentration was in all cases near 6%. Of all four percutaneously applied analgesic preparations, L-4 [6.6% lipid, 2% lidocaine]; L-x [5% lipid, 4% lidocaine]; L-8 [10% lipid, 2% lidocaine]; L-17 [5% lipid, 2% lidocaine] with similar cholate concentrations (mol%), only the transfersomal formulations containing cholate were capable of decreasing the sensitivity of the rat tails to pain. $^*P \leq 0.05$; $^{**}P \leq 0.01$; $^{***}P \leq 0.001$.

watertight wrapping for 25 min. The wrapping was then removed without further manipulation of the skin surface. Skin sensitivity to local pain was then checked by the pinprick method, as described by Gesztes and Mezei (7) and Lubens (3). For this purpose, 10 pricks covering the whole test area were typically performed at 5, 15, 30, 45, 60, 90, and 120 min after removal of the occlusion. If <6 of 10 pricks were felt by the subject, this was taken to be a manifestation of significant local anesthesia.

Acute Toxicity Assay

The median lethal dose of the lidocaine solution and of lidocaine in transfersomes was determined in Swiss albino mice (20–25 g) by using a standard intraperitoneal assay (13).

Results

Results of animal studies with the analgesic transfersomes are summarized in Figures 1–3. Supplementary data on the induction of local pain suppression are given in Table 1.

Heat Sensitivity

Subcutaneous injection of a 2% lidocaine solution increases the response time of a rat's tail to a heat stimulus from 30 to approximately 90 s, but only for some 25 min. This corresponds to a characteristic decay time of analgesic action of approximately 7 min. The lower curve in Figure 1 shows the representative experimental results.

Subcutaneous injection of a liposomal or transfersomal suspension containing a similar total amount of the anesthetic agent gives rise to a complex, biphasic time-course of local analgesia (Figure 1, upper curve). Soon after injection of the analgesic drug carriers into the rat's tail, the first signs of

Table 1. Effect of Transfersomal Composition on the Therapeutic Efficiency of Dermal Analgesic Preparations

	Reaction time(s)[a]		
	5 min	10 min	15 min
Drug solution	31.5 ± 7.5	31 ± 4.5	25 ± 2.5
Transfersome[b]			
S/L = 1:1	44 ± 1.5	37 ± 1	34 ± 1.5
S/L = 1:2	45.5 ± 5.5	36 ± 1	37 ± 1.5
S/L = 1:4	63.5 ± 5.5	71 ± 3	76.5 ± 6

[a] Reaction time of topically anesthetized rats was measured by tail-flick assay as a function of total sodium cholate (NaChol) concentration in the transfersomal preparations containing soybean phosphatidylcholine (SPC) and 2% lidocaine.

[b] Molar ratio: NaChol/SPC = surfactant (S)/lipid (L).

reduced pain sensitivity appear. This strong initial anesthetic effect decays within 6–7 min. It is thus comparable in its temporal dependence to the analgesia caused by a subcutaneous drug injection.

Ten minutes after subcutaneous application of the analgesic vesicles, the intensity of local analgesia begins to increase again. It then reaches a second maximum 5 min later. The characteristic time constants for the onset and decay of such local pain suppression are approximately 10 and 7 min, respectively, as concluded from data analysis by means of Equation (1). Incorporation of the anesthetic drugs into carrier vesicles thus prolongs the drug effects by some 300%, the decay time of drug activity being nearly unaffected.

Dermal application of the lidocaine solution on the intact skin of rats' tails does not induce noticeable analgesia (lowest curve in Figure 2). This is seen from the fact that four subsequent experimental points all show the same hypersensitivity to pain.

Lidocaine-containing standard liposomes are also very poor dermal analgesics. For a period of at least 25 min after the dermal application of a standard liposome suspension, they cause no significant prolongation of the reaction time to a painful heat stimulus (Figure 2, middle curve). Characteristic withdrawal time of approximately 30 s is nearly identical to that measured in the case of NaCl-"treated" animals.

Dermally applied analgesic transfersomes, on the contrary, can induce analgesia rapidly on their topical application to intact skin. The upper curves in Figures 1 and 2 demonstrate this. Rats that have received a local application of such transfersomal analgesics do not react to a painful heat stimulus for >70 s (not shown). This is 130% longer than in controls that have received a placebo or a standard aqueous lidocaine solution. Net prolongation of the corresponding analgesic effect for a variety of transfersomal populations is shown in Figure 3.

The maximal analgesic effect is induced by a dermally applied suspension of transfersomes some 15 min after the drug application. The characteristic onset and decay times, deduced from the experimental data by means of Equation (1), are then 11 and 6.5 min, respectively. At later times, the pain sensitivity is gradually recovered, and the reaction time decreases again; however, a marked analgesic effect is still noticeable even 30 min after the initial drug application.

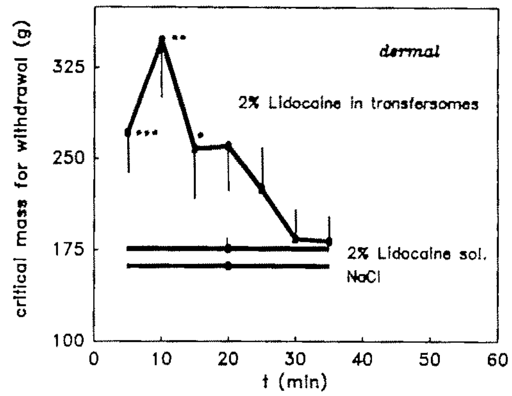

Figure 4. The critical mass that provokes a spontaneous withdrawal of a rat's tail after topical application of various analgesic preparations (Eagle-Carlson test). In contrast to standard lidocaine solutions (sol.), which are analgesically inefficient, the transfersomes containing drugs can decrease the peripheral pressure sensitivity appreciably. $^*P \leq 0.05$; $^{**}P \leq 0.01$; $^{***}P \leq 0.001$.

This shows that the permeation of the analgesic transfersomes through intact skin may cause a delay in the onset of the transferred drug action, although this delay is short. The detailed drug pharmacokinetics thus appears to be determined largely by the intrinsic kinetics of drug action and, in part, by the lidocaine permeation through the transfersomal bilayers. This permeation, as well as the overall drug-transferring efficiency, depends on the carrier composition, as Table 1 illustrates. Table 1 shows that formulations with a very high or very low surfactant concentration are less well suited for induction of local anesthesia than are preparations with an intermediate lipid/surfactant ratio. It should not be forgotten, however, that the overall behavior of a transfersomal drug formulation may also depend on the choice and concentration of the encapsulated drugs.

Pressure Sensitivity

The results of pressure-sensitivity measurements reveal similar trends (Figure 4). Percutaneous treatment of rats' tails with a sodium chloride or 2% lidocaine solution does not result in significant local analgesia. The applied mass that provokes an instantaneous tail-withdrawal reaction in both cases is approximately 175 g. In contrast to this, a percutaneously applied analgesic transfersome suspension increases the corresponding critical mass to approximately 270 g after 5 min and to nearly 350 g after 10 min of drug action. The overall duration of this effect is 30 min, as in the case of the drug-induced reduction of the local heat sensitivity. The corresponding decay times in the former case are somewhat shorter, however.

Induction of Topical Analgesia in Humans

To determine whether our analgesic transfersomes were also active on application to human skin, two groups of volunteers were treated on the intact forearm skin and tested by the pinprick method (3). In this study, only the effects of a single application of drug were tested, which gave rise to a significant but not very persistent local anesthesia. Prolonged pain insensitivity was achieved, however, on repeated drug applications. Clinical applications not reported in this work document this.

Acute Toxicity

The encapsulation of lidocaine in lipid vesicles reduces the overall toxicity of the drug. In our acute toxicity experiments, the 50% lethal doses were found to be 277.3 and 371.0 mg/kg for the free drug and lidocaine combined with lipid vesicles, respectively, the 95% confidence limits being 226.8–339.1 and 301.0–457.3, respectively.

Discussion

Owing to their low molecular weight and high water solubility, most of the standard monomolecular analgesics do not respond to a strong transdermal gradient, nor do they adequately permeate the skin. Thus, analgesics in an aqueous solution, topically applied, do not cross the skin-permeability barrier and thus do not significantly suppress local pain. This is the case before, during, and after evaporation of superficially applied water from the site of application.

Lipophilic analgesics have a somewhat higher chance of achieving the desired therapeutic effect, provided that they are applied under appropriate conditions; however, even with sufficiently lipophilic drugs used in combination with skin fluidizers, the analgesia after a dermal drug application is as a rule rather low.

We have developed a new type of drug carrier that can transport analgesic agents through an intact skin and thus overcome these problems. These carriers are driven by the transdermal hydration gradients (14,15) and were shown to introduce a sufficient amount of analgesic drugs into the cutis and subcutis of a healthy rat tail to cause therapeutically significant relief of local pain after dermal application.

Principle of Operation

In our view, drug carriers must fulfill two basic criteria for a successful transdermal drug delivery effect. If they are to bring an appreciable amount of their payload from the skin surface into the more deeply located skin strata: (a) drug carriers should respond to or create a gradient that drives the drug-carrier complex from the skin surface into the skin interior; and (b) drug vehicles should be able to pass the skin barrier without uncontrollably losing too much of the enclosed therapeutic material.

Transfersomes exhibit good encapsulation as well as a sufficiently potent driving capability to be used as carriers of the water-soluble substances. Transfersome capacity to encapsulate drugs in the present case arises from the fact that the carrier particles used in this study were in the form of a vesicle. Transfersomal drug carriers, consequently, can accommodate anesthetic drugs either in the aqueous interior of a carrier or in the enveloping lipid bilayer for hydrophilic and lipophilic agents, respectively. Carrier penetration is a consequence of the retraction of the transfersomal vesicles from the relatively dry skin surface into the more humid regions of the deeper skin layers (14). All this occurs under the action of the (de)hydration force (16,17). Drug transport in the desired direction is a direct result of this.

Phosphatidylcholine bilayers with added sodium cholate and anesthetic agents appear to be better suited for the purpose of penetration through skin than are pure phosphatidylcholine membranes; this is probably due to their more suitable rheologic and hydration properties. This provides one possible, and plausible, explanation for the observation that only analgesic agents enclosed in suitably optimized transfersomes can reach the subcutaneous tissue spontaneously and with little delay.

We are almost certain, however, that the high drug-carrying potential of the dermally applied transfersomes is not primarily a consequence of stratum corneum fluidization by the cholate molecules. Evidence for this is given in Table 1. If the high therapeutic effect of the analgesic transfersomes was caused by the increased fluidity of the skin lipids, and occurred via the "classical" skin-fluidization route, the degree of therapeutic improvement achieved would have to increase with increasing surfactant/lipid molar ratio. This is not observed, however. On the contrary, the therapeutic effect of the analgesic preparations is relatively low for the micellar carriers with the highest studied surfactant concentration (lipid/surfactant molar ratio 1:1); the drug vehicles with a somewhat lower relative cholate concentration normally perform much better.

It is also unlikely that the therapeutic efficiency of the analgesic transfersomes is due to the fact that

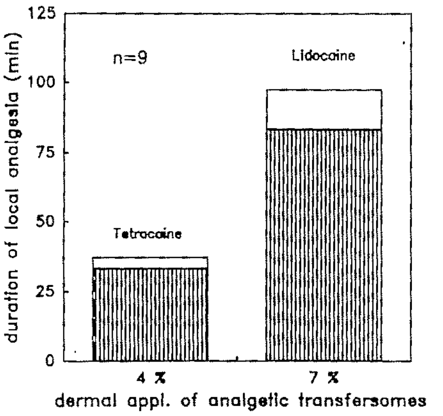

Figure 5. Analgesic effect of two transfersomal preparations with various agents after dermal application (appl.) on human forearms. *Open areas* represent standard deviations.

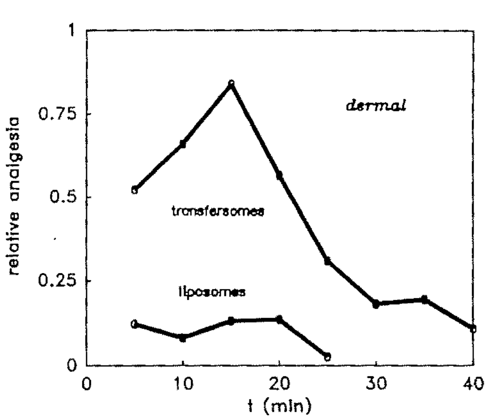

Figure 6. Time dependence of the local, relative analgesia induced by dermally applied lidocaine containing transfersomes or liposomes (normalized net effect). The experimental points were obtained by first subtracting the reaction times measured with lidocaine solution-treated animals from the corresponding data obtained for the transfersome-treated rats and then normalizing the results relative to the longest observed reaction time of 61.2 s. If NaCl-treated animals are taken as a reference, the effect of "analgesic" liposomes is essentially zero (Figure 2).

these carriers have a particlelike appearance. Gesztes and Mezei (7) previously devised a formulation of analgesic "standard liposomes" for dermal applications by using classical galenic recipes. Their preparations thus contained the well-known skin fluidizers propylene, ethyleneglycol, and a fatty acid in combination with the lipid vesicles. The resulting local analgesia after drug application under occlusion was not seen before several hours had passed, however. The absolute efficiency of drug transfer was not reported by Gesztes and Mezei (7) but is likely to have been lower than in our case.

Transfersome-mediated analgesia is not limited to lidocaine molecules as an analgesic agent; this has been confirmed in human studies (Figure 5). It is also not restricted to one type of nociceptor. Different analgesia assays used in this study gave qualitatively similar results. Reduced sensitivity of the topically treated rats to a pressure stimulus (12) resembles closely the corresponding response of similarly treated rats to a heat shock (11) (Figures 3 and 4).

Kinetics of Action

Transfersomal analgesics exert their action more rapidly than other dermal analgesic formulations. In fact, they are nearly as swift in action as an injection needle (Figures 1–4). They are also quantitatively highly efficacious: the integrated effect of percutaneously applied transfersomal analgesics from Figures 1 and 2 can be calculated to exceed 90%.

Consider, for example, the transfersome-induced prolongation of the reaction time in a heat-stimulus assay. To assess this effect, the reaction time of a rat that has been treated locally by receiving a simple lidocaine solution on its tail was subtracted from the reaction time of a rat treated similarly with the appropriate transfersomal analgesic preparation. To clearly distinguish among the relative efficiencies of various therapeutic protocols, all values are here expressed in relation to the corresponding effect elicited by a comparable subcutaneous bolus injection of drug (Figure 1). The latter is assigned a value of 1; in such a representation, the transfersome-mediated local analgesia is obvious.

Liposome-Mediated Prolongation of the Local Anesthetic Action

What about the duration of the transfersome- or liposome-mediated analgesic action? The analgesic effect elicited by subcutaneously applied agents is relatively short-lived. As Figure 1 shows, drug encapsulation into lipid vesicles may improve this by increasing the mean duration of local anesthesia to approximately 0.75 h.

The primary analgesic effect observed immediately after transfersome injection under the skin presumably originates with the nonencapsulated analgesics, which in our case have not been separated from the drug associated with the carrier vesicles. (The fact that the time-course of such first-step analgesia is very similar to the temporal evolution of the analgesia caused by a subcutaneous bolus drug injection corroborates this conclusion.) The prolonged action of the transfersomal analgesics probably results from the gradual drug release from carrier vesicles. Drugs from such carriers reach the skin and the subcutaneous tissues with some delay. Local nociceptors are thus blocked at relatively late times, which gives rise to a more persistent topical analgesia than can be

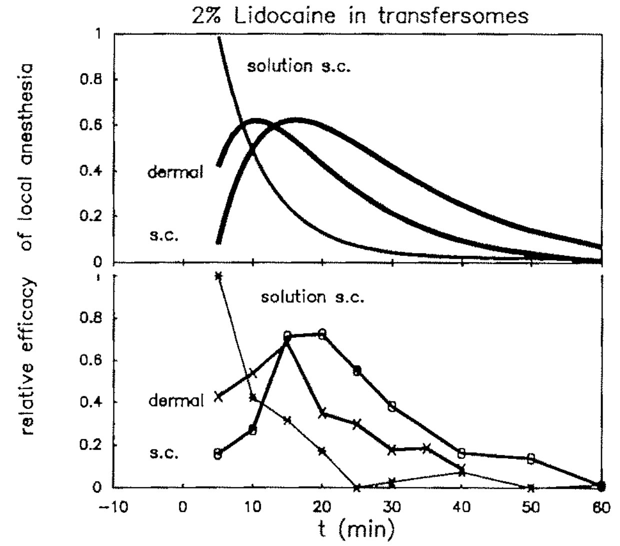

Figure 7. The effective peripheral analgesia caused by percutaneous (dermal) applications of analgesic transfersomes (○), or by subcutaneous (s.c.) injections of lidocaine-containing transfersomes (×); (✻), reference results obtained with lidocaine solution injected under the skin. The *top panel* represents the corresponding model curves, calculated within the framework of biexponential approximation [Equation (1)]. The variable values were t_d = 10.7 min^{-1}; τ_1 = 13 and 6.6 min^{-1}; τ_2 = 10.6 and 10.9 min^{-1}; κ_1 = 11.5 and −3.7; κ_2 = −4.5 and 4, respectively, for dermal and subcutaneous transfersome applications; and τ_1 = 6.7 min^{-1}, τ_2 = 0 min^{-1}, κ_1 = 2, and κ_2 = 0 in the case of subcutaneous lidocaine injections. Optimal carrier vesicles ensure a high degree of topical analgesia that resembles in its overall effect the consequences of a subcutaneous analgesic injection. In the former case, however, the analgesic action sets in with a slight time delay of approximately 10 min, this lag being "therapeutically compensated" in part by the longer duration of the pain insensitivity.

achieved by a subcutaneous drug injection. Of interest, the data from Figures 6 and 7 suggest that the analgesic drug action has a longer duration in the case of a subcutaneous liposome injection than after the dermal application of transfersomal preparations. One possible explanation for this unexpected finding is that the analgesic molecules from subcutaneously injected drug carriers have longer diffusion paths to their target nociceptors than drugs that are applied by means of transfersomes onto the skin surface.

In summary, the antipain effectiveness of dermally applied anesthetic transfersomes has been observed to be similar to that of corresponding subcutaneous injections, provided that similar total drug quantities are used.

Optimally designed transfersomes offer a suitable means for the noninvasive treatment of local pain on direct, topical drug application. By changing the amount and composition of the carriers on the skin surface, the cutis and sometimes even deeper tissues can be desensitized. In humans, complete local anesthesia can be achieved within approximately 30 min by using tetracaine; lidocaine preparations exhibit similar effects after 90 min of dermal action. The resulting local analgesia in both cases lasts for >4 h under suitable conditions (not shown). We believe that this will have far-reaching consequences for the therapy of local pain in humans and animals. It is conceivable that in the future, analgesic transfersomes will be applied safely, routinely, and easily, even by informed patients.

Some questions pertaining to this exciting new type of analgesic therapy remain to be answered, however; for example, the question of the optimal choice of agents and their concentrations, the details of optimal transfersome composition, and the best application mode. Nevertheless, we believe that analgesic transfersomes provide new opportunities in the field of local pain therapy.

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Cesarean Section in a Patient With Unilateral Diaphragmatic Paralysis, Brachial Neuritis, and Pregnancy-Induced Hypertension

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Unilateral diaphragmatic paralysis is usually asymptomatic and rarely requires treatment. When combined with pregnancy-induced changes in pulmonary function, unilateral diaphragmatic paralysis may result in marked respiratory compromise. We present such a case and describe its anesthetic management.

Case Report

A 22-yr-old (gravida 1, para 0) woman with a 36-wk intrauterine pregnancy presented with worsening pregnancy-induced hypertension and increased respiratory distress. Her past medical history was significant for a remote left brachial neuritis and recent mild right brachial neuritis. One month before admission, she noted symptoms of an upper respiratory tract infection that lasted several days. Over the ensuing month, she developed a persistent, nonproductive cough, and increased orthopnea with quick resolution of dyspnea when in the upright position.

Physical examination revealed no breath sounds and dullness to percussion over the right lower lung field, as well as decreased excursion of the right hemidiaphragm on deep inspiration. Chest radiograph showed a 9-cm elevation of the right hemidiaphragm. Spirometry revealed forced vital capacity of 2.24 L (55% predicted), forced expiratory volume in 1 s of 1.91 L (59% predicted), and forced expiratory volume in 1 s divided by vital capacity of 86%. Bronchodilators improved forced expiratory volume in 1 s to 2.3 L (65%). While breathing room air in the supine position, arterial oxygen saturation was 89% and respiratory rate was 30 breaths/min, improving to 98% and 20 breaths/min in the standing position. Postviral unilateral diaphragmatic paralysis was diagnosed, and the patient was treated with inhaled bronchodilators.

One week later, the patient returned with worsening pregnancy-induced hypertension evidenced by a recent 5-kg weight gain to 105.9 kg, arterial blood pressure of 150/100 mm Hg, and peripheral edema. She had a respiratory rate of 30 breaths/min in the supine position. Shortly after admission, she developed right upper quadrant pain, brisk reflexes, and worsening edema. Laboratory results showed increased proteinuria, elevated liver function tests, a platelet count of 220,000/mm^3, and a normal coagulation screen. Intravenous magnesium sulfate was started, and the decision made to deliver the infant. Attempts to induce labor with intravenous pitocin failed, and a cesarean section was scheduled.

In the delivery room, venous access was secured by a 16-gauge peripheral cannula and a central venous pressure catheter. A right radial artery catheter was placed for continuous blood pressure monitoring. Routine monitoring consisted of electrocardiography, pulse oximetry, capnography, and a neuromuscular blockade monitor.

The patient breathed 100% oxygen for 5 min in the supine position, achieving an oxygen saturation of 98%. Anesthesia was induced in rapid sequence with thiopental (250 mg IV) and succinylcholine (100 mg IV) while cricoid pressure was maintained. Arterial desaturation to 65% was noted 45 s after induction. The trachea was intubated, controlled ventilation was initiated, and oxygen saturation quickly increased to 98%. Arterial blood pressure increased from 130/85 to 165/95 mm Hg and was treated successfully with esmolol (50 mg IV), returning blood pressure to 120/70 mm Hg. Anesthesia was maintained with isoflurane (0.5%), nitrous oxide (50%), oxygen (50%), and atracurium (10 mg IV). Oxygen saturation in the supine position remained 97%–98%. A 3.29-kg male, with Apgar scores of 7 at 1 min and 8 at 5 min, was delivered. Cord pH measurement was 7.28. After delivery, anesthesia was supplemented with mor-

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phine (10 mg IV). As the incision was stapled, neuromuscular blockade was reversed with neostigmine (3 mg IV) and glycopyrrolate (0.6 mg IV). Anesthetics were discontinued, and the patient was allowed to breathe 100% oxygen. Arterial desaturation to 65% again occurred while the patient was breathing spontaneously in the supine position. The patient was placed in the sitting position, and arterial saturation improved to 99% after 4–5 min of spontaneous respirations. Arterial blood pressure was stable. Respiratory rate was 12 breaths/min, and chest wall excursion appeared both adequate and bilaterally symmetric. The patient's handgrip strength was vigorous and sustained. The trachea was then extubated in the delivery suite without incident.

The patient was observed in the intensive care unit for 24 h postoperatively and then returned to the maternity floor. On the fourth postoperative day, fluoroscopy revealed persistent right hemidiaphragmatic paralysis. The patient was discharged home on the sixth postoperative day with the following oxygen saturations and respiratory rates: 95% and 20 breaths/min in the sitting position, 93% and 24 breaths/min in the left lateral decubitus position, and 92% and 36 breaths/min in the right lateral decubitus position. Three months after delivery, her symptoms were not improved. She had continued dyspnea on minimal exertion and mild orthopnea. Persistent right hemidiaphragmatic paralysis with possible left hemidiaphragmatic involvement was noted. Planned pulmonary evaluation included a sleep study and measurement of transdiaphragmatic pressures.

Discussion

The etiologies of diaphragmatic paralysis include postsurgical (phrenic nerve transection or damage secondary to retraction or electrocautery); neoplastic (direct phrenic nerve invasion or metastatic involvement); neuromuscular (sequelae of myelitis, encephalitis, polio, diphtheria, multiple sclerosis, herpes simplex virus infection); posttraumatic, mechanical (compression from aortic aneurysms or substernal thyroid); infectious (sequelae of bacterial, viral, syphilitic, or tuberculous infection); and miscellaneous causes, including congenital abnormalities, reaction to antitetanus, and idiopathic factors.

Probably most relevant to our patient are the many reported cases that associate diaphragmatic paralysis with brachial neuritis (1–19). Walsh et al. (1) cite cadaver studies from the 1800s showing that in 44% of patients, the diaphragm was partially innervated by the fifth cervical nerve, thereby illustrating an anatomic "link" between the diaphragm and the brachial plexus. They cite further evidence for such a link via the observations of associated movements between the upper arm and diaphragm after aberrant reinnervation following birth injury, trauma, and neuropathy, as well as by notation of such concomitant impairment after avulsion of the fifth cervical root, birthing, and peripheral neuropathies (1).

The anesthetic management of patients with diaphragmatic paralysis begins with preoperative evaluation. When symptomatic, patients with diaphragmatic paralysis most commonly note dyspnea (worse when supine), cough, and chest wall pain. Most patients with unilateral diaphragmatic paralysis are asymptomatic. Clinical diagnosis can be made using a variety of techniques. At the bedside, paradoxical abdominal motion can be observed. Chest radiograph reveals hemidiaphragmatic elevation and is ideally performed with the patient breathing spontaneously in the recumbent position. Fluoroscopic evidence of paradoxical diaphragmatic motion is noted on sniff and cough maneuvers (Kienboeck's sign). Other diagnostic techniques include measurement of transdiaphragmatic pressures, diaphragmatic electromyography, and diaphragmatic evoked responses with phrenic nerve stimulation. Once the diagnosis is made, the etiology of diaphragmatic paralysis may be ascertained from history, physical examination, and chest radiograph alone. If these fail to suggest the etiology, further evaluation is unlikely to elucidate the cause (20).

The choice of general anesthesia for our patient was based on a consideration of the respiratory effects of conduction blockade superimposed on diaphragmatic paralysis. Advantages of regional anesthesia may include reducing the risk of regurgitation and aspiration of gastric contents associated with general anesthesia in pregnant patients at term. Regional anesthesia may avoid a potentially difficult tracheal intubation in the presence of soft tissue edema secondary to pregnancy-induced hypertension. Epidural anesthesia, in particular, may provide more stable arterial blood pressure control and improved uteroplacental blood flow than a rapid-sequence induction of anesthesia in the setting of pregnancy-induced hypertension (21).

However, the major disadvantage of regional anesthesia, in our estimation, was the potential respiratory consequences of high motor blockade superimposed on a term patient already compromised by a paralyzed hemidiaphragm. In adults, the diaphragm is responsible for 30%–60% of tidal volume. Unilateral diaphragmatic paralysis results in decreased total lung capacity, functional residual capacity, forced vital capacity, and tidal volume, with an increase in respiratory rate and no change in the ventilatory response to carbon dioxide. Diaphragmatic paralysis also causes a compensatory increase in inspiratory rib cage expansion secondary to recruitment of accessory inspiratory muscles. Most important, diaphragmatic paralysis results in a new pattern of more rapid contraction of the remaining inspiratory muscles to compensate for the loss of the diaphragmatic component. Whether this new pattern of contraction is vagally mediated is controversial (22–24).

Accessory muscles of inspiration include the external intercostals, scalenes, sternocleidomastoids, alae nasi, and small muscles of the neck and head. Innervation of the intercostal muscles is via the intercostal nerves, which arise from the spinal cord at the same levels (T-1 to T-11). A high motor blockade would therefore compromise the intercostal component of respiratory compensation in the presence of diaphragmatic paralysis. Freund et al. (25) illustrated that a T-4 epidural motor blockade in healthy patients results in an approximately 58% decrease in expiratory reserve volume. In our patient, high epidural motor blockade would therefore further decrease functional residual capacity, making airway closure and the potential for hypoxemia secondary to ventilation/perfusion ratio mismatch more likely.

The strongest argument for choosing general endotracheal anesthesia and controlled ventilation in this setting is illustrated when changes in forced vital capacity in association with conduction blockade are examined. Tracheal intubation and ventilatory support have been recommended at a forced vital capacity of <15 mL/kg for patients with respiratory insufficiency secondary to other motor disorders (26,27). Preoperatively, our patient's forced vital capacity in the upright position was 2.24 L. Clague and Hall (28) showed an average decrease in forced vital capacity of 19% when patients with right hemidiaphragmatic paralysis were placed supine. A change to the supine position would therefore have reduced our patient's forced vital capacity to approximately 1.8 L. Freund et al. (25) illustrated a decrease in inspiratory capacity of 19% with total thoracic motor blockade. Their data with regard to changes in expiratory reserve volume and inspiratory capacity suggest that high thoracic motor blockade would further reduce our patient's forced vital capacity to well below 1.5 L. We therefore chose general anesthesia to ensure adequate ventilation and gas exchange during the procedure.

Our patient experienced marked and rapid arterial desaturation during induction and emergence from general anesthesia. Several factors contributed to the decrease in oxygen saturation. Oxygen consumption normally increases by at least 20% by the end of pregnancy (29). At term, functional residual capacity is decreased by 15%–20% (30), resulting in an increased shunt fraction, and less oxygen reserve. The normal decrease in functional residual capacity at the end of pregnancy is further aggravated by the supine position and the presence of general anesthesia (31). During normal tidal ventilation, one-third to one-half of supine parturients experience airway closure (30). These changes superimposed on the consequences of a paralyzed hemidiaphragm explain the observed arterial desaturation and prompt improvement with the patient sitting at the conclusion of the procedure.

In summary, we report the successful anesthetic management of a patient with hemidiaphragmatic paralysis and pregnancy-induced hypertension undergoing cesarean section. Neither term pregnancy nor unilateral diaphragmatic paralysis alone would have detrimental respiratory implications in most patients, but the combination presents a situation in which the potential for pulmonary decompensation is significant.

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Intraosseous Infusion: Elective Use in Pediatric Anesthesia

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The intraosseous (IO) route for parenteral access is increasingly being used for resuscitation of infants and children (1). Only one case has been documented in the recent anesthesia literature (2) representing a last resort during cardiopulmonary resuscitation. We report elective use of IO parenteral infusion for induction and maintenance of anesthesia in an infant with no readily available intravenous (IV) access.

Case Report

A 3-mo-old male child was scheduled for revision of a ventriculoperitoneal (VP) shunt. The shunt had been inserted 2 wk earlier but had apparently become disconnected at the reservoir, because cerebrospinal fluid was collecting beneath the scalp, adjacent to the incision.

The patient was a low-birth-weight term infant born at an outlying hospital by normal sinus vaginal delivery after an unremarkable gestational history. Cyanosis and respiratory distress dictated early endotracheal intubation and mechanical ventilation. Echocardiogram and cardiac catheterization revealed multiple cardiac anomalies, including a single left ventricle. Pulmonary artery banding was performed after administration of furosemide and digoxin failed to control progressive cardiac failure. After transfer to our hospital at 18 days of age, he underwent patent ductus arteriosus ligation and removal of the pulmonary band. His prolonged intensive care unit course was complicated by chronic bilateral upper lobe collapse requiring intensive chest physiotherapy, frequent nebulization, and, eventually, bronchoscopy under general anesthesia.

Seizure activity prompted a magnetic resonance imaging scan that revealed large ventricles and cerebral atrophy. The first attempt to place a VP shunt was canceled after several experienced anesthesiologists were unable to establish venous access. The shunt operation was performed the following day after a brachial venous catheter was placed by cutdown, which was the third site attempted that day.

Two weeks later, the patient was scheduled for VP shunt revision after radiographs revealed a disconnection at the cranial reservoir. Because cerebrospinal fluid was extravasating subcutaneously and the patient had a palpably soft fontanelle, he was not thought to have increased intracranial pressure. He received medications and maintenance fluids by nasogastric tube until 2 h before his scheduled operating room time.

A pediatric bone marrow needle was obtained from the emergency department, and a plan was discussed with the surgeons to pursue IO line placement if reasonable attempts at peripheral line placement were unsuccessful. Intraosseous access, including possible complications, was then discussed in detail with the patient's parents.

In the operating room, peripheral IV placement was attempted in all four extremities for 20 min, at which time the decision to use the IO route was made. The needle was placed in the proximal tibia under sterile conditions, requiring 5 min for completion. An intramuscular injection of ketamine and glycopyrrolate had been given before bone marrow puncture, although IO needle insertion can be performed in an awake patient using local anesthetic infiltration. Once access was established, lactated Ringer's solution (10 mL/kg) was administered, followed by pancuronium (0.1 mg/kg) and 5 mL of saline solution flush. Neuromuscular blockade was considered adequate at 180 s by loss-of-twitch response. After intubation, the case proceeded uneventfully, with maintenance fluids and antibiotics delivered by IO route. Reversal of neuromuscular blockade was accomplished through the bone marrow needle, and the trachea was extubated in the operating room. The IO line was maintained in the recovery room for continued delivery of fluids and an additional dose of antibiotics. The line was discontinued soon after the patient's arrival at the ward.

No complications of IO infusion were seen. The child's pulmonary status, although continuing to require vigorous chest physiotherapy and frequent

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nebulization, was unchanged from what it had been preoperatively. The patient was discharged from the hospital 11 days after the VP shunt revision.

Discussion

This case represents an example of an increasing number of infants and children who undergo multiple surgical procedures or long intensive care unit courses and present with impossible IV access. Our patient had occupied an intensive care unit bed for 10 of his 12 wk of life. Central line history included bilateral catheterization of internal and external jugular veins, subclavian veins, and femoral veins. His primary physicians strongly advised against further attempts at percutaneous central venous access because of his complex cardiac anatomy and a history of failure to cannulate the jugular or subclavian vessels. The surgical staff had attempted femoral vein catheterization multiple times on both sides the evening before surgery without success. Multiple cutdowns had previously been carried out on all four extremities, including the femoral veins. A brachial cutdown had been successful 2 wk before this operation but was the third site and required 1.5 h to complete. The number of peripheral venipunctures could conservatively be estimated to number 100–200 over the course of his hospitalization. We believed that IO infusion was the better alternative to a difficult and prolonged venous cutdown in a patient whose polycythemia (hematocrit 56%) would place him at considerable risk if allowed to become hypovolemic.

Intraosseous infusion for the purpose of fluid resuscitation was first described by Doan (3) and Drinker et al. (4) in 1922. Successive reports from the 1930s and 1940s detailed indications, methods, and complications (5–11). The primary indication was for simple fluid resuscitation in infants and young children in whom IV access was difficult. The current use of IO infusions is only a few years old. Its resurgence in popularity filled a clinical need for rapid access to the intravascular system in neonates who would die without immediate infusions of fluid or medications, or both. This rebirth and subsequent reevaluation has been primarily documented in the emergency medicine literature (12–23).

Elective use of IO infusion for induction and maintenance of anesthesia has not been previously reported. Current uses include access during cardiac arrest, shock, extensive burns, and major trauma. Further indications include administration of diazepam and phenytoin for seizure control, continuous administration of dopamine and dobutamine for inotropic support, antibiotics for presumed sepsis, insulin for diabetic ketoacidosis, and administration of a variety of other drugs (16,18,24–28). Use of the IO route has been anecdotally reported for airway management (15,16). Intraosseous succinylcholine can be utilized for airway control in patients with status epilepticus, combative head-injured patients, and pediatric burn patients, and thiopental administration has also been described (15,24). Clinical time to onset of action after IO infusion of several drugs, notably succinylcholine, atropine, and diazepam, has been reported previously (15,16,24). Animal studies have analyzed plasma levels for succinylcholine, atropine, diazepam, and phenobarbital comparing IV, IO, intramuscular, and endotracheal routes (12,17,18). Moore et al. (17) recorded the time to respiratory arrest and loss of forefoot twitch after IV, IO, or endotracheal administration of succinylcholine (1.0 mg/kg) in sheep. Comparing IV with IO infusion, they found that respiratory arrest was delayed by approximately 27 s in the IO group (30.8 ± 7.3 [IV]; 57.5 ± 10.3 [IO]), whereas time to 100% loss of forefoot twitch was slower in the IO group by only 7.5 s (93.3 ± 34.0 [IV]; 100.8 ± 24.2 [IO]). These studies compared favorably with our clinical finding of virtually no delay in relaxation for pancuronium.

The medullary cavity in long bones is composed of a network of venous sinusoids that drain into a central venous canal. Blood exits the venous canal via nutrient or emissary veins into the systemic venous circulation. Children <5 yr old have a highly vascular and primarily cellular marrow; however, after 5 yr, the marrow cavity becomes less vascular and is characterized by more adipose tissue than cellular elements. Fluids delivered via an IO infusion can achieve significant flow rates. Shoor et al. (27), using a 13-gauge needle in a bovine model, obtained flows of 10 and 40 mL/min under gravity and 300 mm Hg of pressure, respectively. Gravity infusion in the infant tibia can typically average >100 mL/h (29). The technique has been reported to be used in the femur, tibia, iliac crest, and sternum. Preferred insertion sites in children include the proximal and distal tibia and the distal femur (1,2,14,23). The proximal tibia is generally agreed to be the optimal site because it has a broad, flat surface covered by a thin layer of skin. However, at ages >5–6 yr, the proximal tibia becomes much thicker and harder to penetrate, making the distal tibia preferable. When using the proximal tibia, the tibial tuberosity is palpated and a point is selected in the midline on the anteromedial, flat surface, 2–3 cm below the tibial tuberosity. The needle is inserted at an angle of 60°–90° away from the epiphyseal plate to avoid any damage. The bevel should point away from the joint space, and a rotary motion is applied, similar to that used for a bone marrow biopsy. Aspiration of bone marrow confirms proper placement.

Use of the IO route for induction and maintenance of anesthesia was suggested in the 1940s–1950s (10); however, this method should not be used routinely in cases of difficult pediatric IV access before considering a number of potential problems. Of the complications associated with IO infusion, extravasation of fluid around the puncture site is the most common. If the extravasated fluid is crystalloid, this presents no problem; however, if it is sodium bicarbonate or some other alkaline agent, local tissue damage may occur. Of more concern is the risk of osteomyelitis and cellulitis. Rosetti et al. (30) reviewed the literature from 1942 to 1977 and found only 27 reported cases of osteomyelitis in >4000 IO infusions. This rate of 0.6% compares favorably with a 3.7% incidence of local infection associated with the use of venous cannulas (31). In addition, the reports of osteomyelitis are from 40 yr ago, before the use of broad-spectrum antibiotics, and involved IO infusions of long duration and of hypertonic solutions. There have been no cases of osteomyelitis reported in the recent literature subsequent to the use of IO infusions. Many physicians are concerned about possible damage to the epiphyseal plate and bone marrow elements. However, there has never been a reported case of damage to the epiphyseal plate, and no lasting negative effects have been identified in multiple clinical and experimental trials (1,14). Potential injury to the growth plate can be avoided by taking care to palpate bony landmarks and to place the needle away from the joint space.

Fat or bone marrow emboli have been regarded as potential complications, but no cases have been documented. Heinild et al. (5), using postmortem examinations of patients, reported no evidence of fat emboli in approximately 1000 pediatric infusions. More recently, Orlowski et al. (26) found a high incidence of fat and bone marrow emboli in the lungs of a canine model subsequent to IO infusion. Ventilation-perfusion relationships, assessed by analyzing arterial blood gases in these animals, failed to reveal any significant change, even though the incidence of bone marrow or fat emboli in pulmonary blood vessels was found to be as high as 4.48 emboli/mm^2. The same authors also reported anecdotally that bone marrow emboli were found in the lungs of two infants who died after major resuscitation episodes, including IO infusions. Whether this data can be applied to humans not undergoing cardiopulmonary resuscitation and not subject to the forces of external cardiac massage is unknown. However, the authors chose to recommend that this technique not be used in patients with intracardiac right-to-left shunts, referring to the theoretically increased morbidity associated with systemic emboli of any type. A recent review article (1) mentioned the possibility of fat embolism but dismissed its importance, pointing out that the marrow of children is relatively fat free. This article did not include children with intracardiac shunts in its list of absolute contraindications (osteogenesis imperfecta, osteopetrosis, and ipsilateral fractured extremity).

For relatively short procedures, IO infusion should be considered by anesthesiologists for cases of extreme difficulty in obtaining IV access in children <5 yr old; however, until further work is done to determine the true incidence of fat and cellular bone marrow embolization, the list of relative contraindications must include the presence of an intracardiac right-to-left shunt and severe pulmonary insufficiency. Although our patient had both of these problems but suffered no detectable complications from IO infusion, we recommend its use only after careful consideration of the risk/benefit ratio in patients like ours.

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Seizures and Opisthotonos After Propofol Anesthesia

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Seizures occurring after general anesthesia are a rare event, and opisthotonos even more rare. Since its introduction in the United Kingdom in June 1986, there have been several reports in the European literature of seizures and opisthotonos occurring after propofol anesthesia. Similar sequelae have yet to be reported in North America. Two cases are described of seizurelike activity associated with opisthotonic posturing that occurred in patients in our ambulatory surgery unit after they received propofol anesthesia.

Case Reports

Patient 1

A healthy 34-yr-old, 85-kg man without a history of alcohol or drug use underwent arthroscopy and menisectomy of his left knee. Anesthetic induction consisted of intravenous midazolam (2 mg) and *d*-tubocurarine (3 mg), followed 3 min later by propofol (2.4 mg/kg). Endotracheal intubation was facilitated by intravenous succinycholine (1.5 mg/kg). Anesthesia was maintained with 70% N_2O in O_2 and propofol infused at 200 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 15 min, then 150 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for an additional 30 min. Intravenous atracurium (20 mg, plus an additional 10 mg) was administered initially to facilitate controlled ventilation. After 40 min, spontaneous respiration was assisted with end-tidal CO_2 measured at 38 mm Hg. Muscle relaxant reversal was not deemed necessary at the end of surgery because the train-of-four ratio was 4/4, and unassisted respiratory effort and gas exchange were normal (end-tidal Pco_2 37–40 mm Hg). Intravenous ketorolac (60 mg) was administered for postoperative pain control, and the propofol infusion was discontinued 15 min before the trachea was extubated. The surgery was complicated by dissection of the isotonic irrigation fluid through the capsule of the knee, with approximately 1 L of lactated Ringer's solution extravasated within the tissues of the upper left thigh.

The vital signs recorded on arrival in the recovery room were blood pressure (126/96 mm Hg), heart rate (68 beats/min), respiration (18 breaths/min), oral temperature (35.6°C), and oxygen saturation (96% on mask oxygen at 8 L/min). Approximately 2 min later, the patient had a generalized, tonic-clonic seizure that was temporarily ablated with intravenous midazolam (5 mg). Within 5 min, a second and then a third seizure, each lasting 1–2 min, were observed. Extension posturing of the head and neck immediately preceded and accompanied each event. The trachea was reintubated after intravenous thiopental (75 mg) and succinylcholine (80 mg). Spontaneous ventilation resumed within 10 min while 50% oxygen was administered through the endotracheal tube. The possibility of hyponatremia or hypoglycemia was excluded by normal electrolyte and serum glucose test results. An arterial blood gas sample drawn just after the first seizure revealed pHa 7.39, $Paco_2$ 40 mm Hg, Pao_2 142 mm Hg, and hemoglobin level 14.3 g/dL. Auscultation of his chest was clear, with no wheezes or rales; he remained hemodynamically stable and well oxygenated for the entire episode. He was admitted to the University Hospital, where head computed tomography scan and electroencephalogram test results were unremarkable. Serum toxicology tests taken just after transport to the hospital showed no evidence of alcohol or illicit drug use. No further seizures were observed, and his sensorium cleared over 4–5 h. The fluid in his left thigh rapidly mobilized, and there was no indication of excessive circulatory volume or electrolyte imbalance. He was observed in the hospital overnight and discharged the next morning.

This patient had been involved in a motor vehicle accident 15 yr earlier and had sustained a closed head injury from which he fully recovered. He denied any personal or family history of a seizure disorder.

Patient 2

An athletic 18-yr-old, 55-kg woman presented for diagnostic arthroscopy of the left knee. Anesthesia

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was induced with intravenous midazolam (2 mg) and *d*-tubocurarine (3 mg), followed 3 min later by propofol (2.5 mg/kg) and succinylcholine (1.5 mg/kg) to facilitate endotracheal intubation. The anesthetic maintenance consisted of 70% N_2O in O_2 and propofol infused at 200 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 10 min, then decreased to 120 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 15 min. After endotracheal intubation, atracurium (20 mg IV) was administered to control ventilation, maintaining end-tidal CO_2 at 35 mm Hg. Intravenous ketorolac (60 mg) was administered to help manage postoperative pain. Vital signs and pulse oximetry readings were within normal limits during the operation. At the conclusion of surgery, the neuromuscular block was reversed with edrophonium (25 mg) and atropine (0.5 mg), and a normal ventilatory pattern was confirmed. After an uneventful tracheal extubation, the patient was transported to the recovery room.

The patient's emergence from the anesthesia was unexpectedly delayed, because she remained unconscious for >1 h in the recovery room with normal vital signs and pulse oximetry readings of 98%, with supplemental mask oxygen at 40%. She then awoke and seemed to respond appropriately for approximately 2–3 min, when she abruptly became restless and confused and exhibited pronounced athetoid movements of her head, neck, and limbs. She was given intravenous nalbuphine (10 mg), followed 5 min later by diphenhydramine (25 mg) to ameliorate what was thought to be an extrapyramidal type of dystonia. These drugs served only to temporarily sedate her. Approximately 15 min later, she reawakened more restless than before. Her arterial blood pressure increased to 140/100 mm Hg, and her pupils were widely dilated; but her heart rate and oximetry readings remained stable at 58 beats/min and 99%, respectively. Her agitation and abnormal posturing continued to worsen, progressing to frank opisthotonos with interspersed tonic-clonic seizurelike activity. Her trachea was reintubated after administration of intravenous propofol (90 mg) and succinylcholine (60 mg), and ventilation was assisted with a Jackson-Reese circuit and 100% O_2 during transport to the University Hospital. The patient continued to manifest extension posturing and seizurelike movements, which were temporarily suppressed with three additional bolus doses of propofol (20–30 mg IV) while in the ambulance.

In the emergency room, the opisthotonic posturing became severe, and she was given two intravenous doses of thiopental (75 mg) followed by midazolam (5 mg) by bolus and then by infusion at 4 mg/h overnight, which suppressed all abnormal movements. Head computer tomography scan and spinal fluid analysis were normal. Because of the severity of the opisthotonos, the patient received intravenous midazolam before an electroencephalogram could be obtained. The next morning, after the trachea was extubated, the patient was oriented and cooperative, with no recollection of the postanesthesia events. She developed a postdural puncture headache after a diagnostic spinal tap, which was relieved 2 days later by a lumbar epidural blood patch. She has since returned to normal activities. She has no personal or family history of a seizure disorder and denies any alcohol or illicit drug use.

Neither patient received local anesthetics nor opiates in the operating room, and the second patient was given a single dose of nalbuphine only after the onset of her problems in the recovery room.

Discussion

Seizures occurring during surgery often coincide with the administration of a specific anesthetic, whereas postoperative seizures are more commonly attributable to nonanesthetic causes. This does not seem to be the case with propofol, where the majority of neurologic complications reported to date, other than the minor muscle twitches seen during induction of anesthesia, have developed in the recovery period. Specifically, opisthotonos, previously a rare phenomenon in anesthetic practice, has been a recurrent finding in case reports from the European literature (1–6) and is listed in the packaging insert as a possible adverse reaction. The Committee on Safety of Medicines (the British regulatory body equivalent to the Food and Drug Administration) has received 37 reports of seizures, many accompanied by opisthotonic posturing thought to be due to propofol. Thirteen of these patients are known epileptics, which may represent a population at relative risk. The manufacturer has knowledge of six cases in the United States involving opisthotonos, myoclonia, and seizurelike behaviors that were spontaneously reported to them during the period of November 1989 to the present (personal communication with ICI/Stuart Pharmaceuticals, April 21, 1992). From this information, it appears that the incidence of severe postoperative myoclonic sequalae requiring intervention is very low.

The mechanism by which propofol may act to produce these neurologic events is unclear. As pointed out by Modica et al. (7) in their recent review of the pro- and anticonvulsant effects of anesthetics, what we observe clinically as a "seizure" may or may not represent the high-voltage electrical discharge characteristic of true cortical seizures. Without electroencephalographic monitoring, they conclude, "it is extremely difficult to determine whether abnormal appearing seizure-like muscle movements are due to epileptiform activity or nonepileptic myoclonia." Opisthotonos, for instance, is rarely seen with cortical epilepsy but is a form of acute dystonic reaction that may be seen after administration of phenothiazine-type drugs acting at subcortical sites. Indeed, there is some evidence in a mouse model that propofol exerts effects at these deeper structures (8). Yet, Hodkinson et al. (9) reported three patients undergoing electrocorticographic mapping of seizure foci who developed true cortical epilepsy after a bolus dose of propofol (2 mg/kg). In each instance, they observed complexes consisting of spikes, polyspikes, and spike and slow waves commencing 20–30 s after injection and persisting for up to 7 min. In contrast to these data, Lowson et al. (10) studied the protective effects of propofol against electrically and chemically induced seizures in mice and concluded that propofol possesses strong anticonvulsant properties. Propofol also diminishes seizure duration during electroconvulsive therapy in humans (11,12). Like other drugs that manifest both pro- and anticonvulsant activity, such as barbiturates, ketamine, enflurane, and etomidate, propofol has been used successfully to ablate status epilepticus refractory to other therapy (13,14).

Although the dose of propofol used in our two patients tends toward the upper limit usually used in clinical practice, a review of the published literature fails to demonstrate a specific dose-response relationship to the events we are reporting. Although most of these patients, including the two discussed in this report, displayed only brief episodes of postanesthetic abnormalities, there have been reports of prolonged difficulties that cannot be directly related to the short hypnotic action or rapid elimination from blood of propofol. Hopkins (4) documents a case of a 29-yr-old woman who received 150 mg of propofol (2.5 mg/kg) and suffered apneic attacks, recurrent seizures, and opisthotonos for 23 days postoperatively. Another woman from Denmark reportedly had seizures for 7 days after propofol anesthesia despite antiepileptic medications (15).

This leads some to speculate that a metabolite may be at fault. To our knowledge, none of the known metabolic by-products (several propofol glucuronides and the 4-sulfate conjugates of 1,4-quinol) are epileptogenic.

We report these two cases to raise the awareness of anesthesiologists to the possibility of seizurelike activity and opisthotonos associated with the use of propofol in combination with many anesthetic techniques. Many anesthetic and analgesic drugs are known to produce seizure activity clinically, but the emergence of opisthotonos, and a variety of other athetoid behaviors in the postoperative period, is almost uniquely associated with the use of propofol. The adjuvant drugs used during anesthesia were administered in small quantities, whereas the propofol was infused at rather high doses. We noted a striking exacerbation of symptoms in our second patient after administration of repeated boluses of propofol during the recovery period. Also, propofol is implicated in a number of similar reports from Europe, where it has been in clinical use since 1986. Although clinical evaluation of these two patients does not conclusively demonstrate the administration of propofol to have caused the neurologic aberrations we report, we could not find other likely explanations. Unfortunately, the current paucity of information with regard to these phenomena and how they may relate to different dosages and methods of administration of propofol, as well as differences in patient populations, makes it difficult to draw definitive conclusions or make treatment recommendations.

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Letters to the Editor

Sympathetic Dystrophy: New Name, New Concepts, New Treatment?

To the Editor:

We have read with interest the preliminary results by Vanos et al. (1) about the use of ketorolac in patients with sympathetic maintained pain (formerly sympathetic reflex dystrophy). We agree that it is compulsory to perform prospective, controlled and double-blind studies before accepting this new treatment. An excessive production or response of some prostaglandins in this type of pain is supported by more scientific data. Perhaps prostaglandin-induced hyperalgesia is mediated by a presynaptic (postganglionic sympathetic neurons) release of prostaglandins stimulated by norepinephrine (2,3). Taiwo et al. (4) reported the direct effect of cyclic adenosine monophosphate as second messenger in peripheral hyperalgesia in primary afferent nociceptors. Also they suggested that it could be the final common pathway for many agonists in nociception, including the direct acting prostaglandin E_2. In another publication, the same authors (5) demonstrated the blocking effect of morphine (by stimulation of μ-receptor in the primary afferents) on prostaglandin E_2's induced hyperalgesia, but not on the intracellular effects of 8-bromo cyclic adenosine monophosphate (a cell membrane diffusible cyclic adenosine monophosphate analogue). Kimbal (6) has described a new scheme to understand the interaction of physiologic products in neurogenic inflammation that binds prostaglandin E_2, interleukin (IL), histamine, bradykinin, and others, all linked to substance P. Regarding sympathetic maintained pain, IL-8 could have a direct pain generating role successfully blocked by antiadrenergic drugs, but not by the cyclooxygenase inhibitor. Cunha et al. (7) proposed that IL-8 could be an intermediator between tissue damage and sensitization of pain receptors, leading to the development of sympathetic hyperalgesia.

Recently, Drummond et al. (8) challenged the classical conceptions of sympathetic maintained pain as being an increase of sympathetic outflow in the diseased limb. Instead they observed a decrease of 3,4-dihydroxyphenylethyleneglycol and catecholamines in venous samples of affected limbs in patients diagnosed with sympathetic maintained pain, therefore, probably finding a decrease in sympathetic outflow!

If sympathetic control is still the probable main factor in the physiopathology of sympathetic maintained pain, several other mediators (as suggested above) could also be involved. That could explain the usefulness of treatments different than sympathetic blockade.

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Wet Tap Due to Epidural Needle Defect

To the Editor:

Most anesthesiologists use the loss of resistance technique to locate the appropriate endpoint when placing an epidural catheter. Soft interspinous ligaments or a leak at the Luer lock between the syringe and needle may cause a decrease in resistance below the expected amount. This case demonstrates another cause of decreased resistance and reminds us to inspect and test the whole syringe-needle unit for integrity before starting the procedure.

Recently, on our chronic pain service, we evaluated a 47-yr-old woman with syringomyelia and a spinal cord injury resulting from a complication during biopsy of her thoracic syrinx. She presented with severe right-sided pain refractory to all employed modes of therapy and was to undergo a trial of continuous epidural narcotic therapy. For the epidural placement, the patient was placed in the sitting fetal position with her feet on a chair, and with head down on her bedtable to provide maximum thoracic kyphosis. After betadine preparation and 1% lidocaine infiltration

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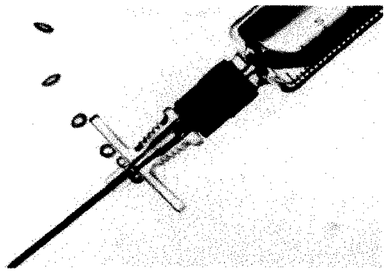

Figure 1. Underwater leak test shows rising air bubbles from the defective junction of the metal and plastic parts of the epidural needle.

of the skin and subcutaneous tissue at the T7-8 interspace, a 17-gauge Tuohy needle (Arrow Inc.) was placed easily into the interspinous ligament. Using the loss of resistance technique with a 3-mL volume of air in a 5-mL lubricated glass syringe, the needle was carefully advanced. During needle advancement, an unusually low resistance was felt in the plunger. The syringe-needle connection was confirmed secure. The first two attempts at finding the epidural space were unsuccessful and were without complication. On the third attempt, the same unusually low resistance was encountered, and despite efforts to the contrary, the dura was punctured and significant wet tap obtained. The needle was quickly removed. At this point, a new epidural needle was used, a new interspace chosen, and the needle was easily placed in the epidural space without complication. The epidural narcotic trial went well but the patient suffered a severe postdural puncture headache.

Immediately after the original needle was removed from the patient, the attending anesthesiologist examined it and placed it in a water bath, where under positive pressure, an air leak was noticed at the junction of the plastic hub and metal needle shaft. This is shown in Figure 1. The defect was large enough to cause the change in ligament resistance we observed.

In view of our experience, it may be worthwhile to check the needle-syringe combination for such defects before using the needle by occluding the needle tip with a sterile gloved finger and applying pressure to the syringe plunger.

A review of the literature did not reveal any previous reports of this complication.

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Tongue Numbness as the Early Sign of 2% Lidocaine Intravenous Epidural Catheter Migration

To the Editor:

The interesting case report by McLean et al. (1) of intravascular migration of an epidural catheter despite multiple test doses and techniques emphasizes the importance of early clinical observation of intravenous injection of lidocaine.

Four years ago, we described a case in which tinnitus was the early diagnostic sign of intravenous injection of 0.5% bupivacaine (2). We now report a case in which tongue numbness expressed itself as the early sign of 2% lidocaine intravenous injection through an epidural catheter.

A 30-yr-old parturient in her second gestation was brought to the operating room for cesarean section because of no progress of labor. Three years earlier, she had had epidural analgesia for delivery of twins. However, because of difficulty with delivery of the second newborn, she was rushed to the operating room, where the second newborn was delivered via cesarean section under general anesthesia. She then required 8 U of blood because of disseminated intravascular coagulation.

On the present occasion, an epidural catheter was inserted through the L3–4 interspace while another spinal injection was performed at L2–3 with 1.5 mL of 0.5% bupivacaine. However, there was no indication of spinal anesthesia 15 min later despite cerebrospinal fluid that had been flowing through the 25-gauge spinal needle before the anesthetic was injected. Then, 5 mL of 2% lidocaine was injected through the epidural catheter. Five minutes later, the patient complained of dizziness and tingling in her tongue. This sensation passed after another 5 min. Then, another 4 mL of 2% lidocaine was again injected through the epidural catheter, which elicited the same sensation of dizziness and tongue numbness. There were no signs of seizures or difficulty in breathing. Intravenous migration of the epidural catheter was determined to be the cause; the patient's trachea was then intubated and cesarean section performed under general anesthesia. Blood at the epidural catheter orifice was found after its removal at the end of the operation.

McLean et al. (1) stated that there was no change in mental status until the occurrence of the grand-mal seizure after the administration of 18 mL of 2% lidocaine with 1:200,000 epinephrine and 100 mg of fentanyl. Perhaps the addition of fentanyl or epinephrine obscured the early signs of lidocaine toxicity.

I propose the use of 2% lidocaine alone as a test dose through the epidural catheter and the search for tongue numbness as the early clinical sign of intravenous 2% lidocaine injection through a migrated epidural catheter.

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Two Cheers for Anesthesiology Journals, 1992: A Reply to Greene

To the Editor:

Greene's perceptive article (1) about anesthesiology journals, like Keats' earlier one about monitoring (2), is an example of the true purpose of academia: to challenge perceived wisdom (3). He is not the first to question where our sagging anesthesia library shelves are leading us; Duncan and Cohen (4) concluded that "the literature has become too confined in scope and reductive in reasoning."

Greene's analysis was somewhat incomplete in ignoring the reasons for the increase in publications. Certainly, as he suggests, the publishing houses are partly responsible, but they are only supporting a need—the need for anesthesiologists to prove themselves by publishing papers or, for that matter, by serving as editors or on editorial boards. It is part of the wider academic culture that encourages spurious publication to obtain grants and promotions rather than to communicate with others (5); and so long as pharmaceutical companies provide easy funding for clinicians to test their products, we are unlikely to reduce the number of pages devoted to trivia, the second form of what Greene aptly describes as "space-occupying lesions."

Anesthesiology is not alone in these difficulties; the whole of clinical medicine, even the whole of science, seems in danger of drowning in a sea of irrelevant and ever more reductionist information. Greene asks us not to "hide within a sub-subspecialty," but this is also happening to the rest of science. In 1990, the *Lancet* received more than 100 new journals (6). In this week's (April 2, 1992) issue of *Nature*, there are advertisements for these new journals: *Nature Genetics, Human Molecular Genetics, Molecular Phylogenetics and Evolution, Biological Signals,* and *Cellular Physiology and Biochemistry*. Sommer (7), reviewing *DNA Sequence: The Journal of DNA Sequencing and Mapping,* wrote, ". . . I anticipate it will soon spawn a companion journal, *RNA Sequence,* which in turn will spawn *Codon* and *Untranslated Regions*. Such is the nature of progress." That issue of *Nature* (October 3, 1991) included advertisements for *Quality of Life Research, Minimally Invasive Therapy, Gynaecological Endoscopy, Neurodegeneration,* and *The Breast,* selected from many others as at least being directly relevant to clinical medicine.

A specialty that has to remain as generalist as anesthesia is bound to suffer from these superspecializations. It will suffer in the clinical sphere, as clinicians peeling off their ever more specific disease interests come to regard the generalists as amateurs, and in the scientific sphere, as the present equating of grant money with measurement of research success downgrades everyone unable to get a piece of the action in "big science."

Nevertheless, I agree with Greene: we must be courageous and remain generalists. One day our time may come; reductionism is fashionable but has no sole rights to truth. It is worth remembering that public health medicine has saved more lives than DNA manipulation is ever likely to do.

What disappoints are Greene's defeatist solutions, which amount to little more than resigned capitulation. The present state of reviewing is anarchic and self-gratifying; there is a "growing army of review writers" (8), and a "large proportion of the research community must be writing, or have recently written, a review" (9). Review and meta-analysis (10) are important and are, I believe, the only way for busy clinicians to make sense of research findings. Reviewing must be as scientific as the original research is supposed to be, and there must be funding (11) to enable qualified people to review and analyze as part of their recognized work instead of yet another extra that they do, often for paltry commissions.

Greene's suggestion that we shall all simply have to resign ourselves to more reading is unacceptable. We do not have the time. Greene's figures for number of issues of anesthesiology journals by decade fits the exponential equation $y = 6.36 \times 10^{0.017x}$ (where y is number of issues, x is year, and 1922 is taken as year 1); the correlation coefficient is 0.996. (Of note, the exponent is nearly the same as for growth in the total number of biomedical journals [12].) If this rate of growth continues, the resident of today, who has 98 issues to read each year, will have 224 to read in the year 2012 and 332 to read as retirement approaches in the year 2022. That is without the intensive care journals, pain journals, general medical journals, general scientific journals, journals of other interests (I subscribe to the *Journal of Medical Ethics*), newspapers, and news magazines—these last of importance because we are a part of the community in which we care, as Greene humanely put it, "for the entire patient, not just part of him or her."

Medical knowledge is expanding faster than anyone can keep up with, but we are perhaps deluding ourselves by pretending that it is so very important. In parts of Africa the mortality rate in the first year of life is more than 150 per 1000 live births. If people's lives are really to improve, they need better social conditions.

Some, including the editor of *Nature* (13), think that the new technology will be an influence for sanity in scientific publication, but I withhold judgment; publication could just as easily become more unmanageable and even less controllable (or definable?), even if more readily accessible. We may not succeed, but anesthesiologists and other generalists have an important part to play in keeping medical feet on the ground. We are less able to do that if we have less time to lift our heads and look around us. We cannot directly control publication, but we can examine critically the driving forces and ask whether they cannot be curbed.

Faced with more journals and more issues of those journals, the only sensible solution is to be more selective in what we read. The most important of Greene's five ways of change was the second: to learn and teach the skill of interpreting what is written and to select sensibly what to read.

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Anesthesiologist's Interactions With Other Medical Departments Outside the Operating Room

To the Editor:

We read with interest the article by Cheng et al. (1). Their survey has formally called to our attention a problem that affects many institutions and, to a great extent, directors of departments of anesthesia. As the representative of the American Society of Anesthesiologists to the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) Hospital Professional and Technical Advisory Committee (B.S.E.), and as Vice President for Research and Standards, JCAHO (P.M.S.), we have been confronted with questions about the issues addressed by Cheng et al. and believe that some of their statements and interpretations need clarification.

On page 274, second paragraph, they state that, "the director of anesthesia services is responsible for *developing* [italicized for emphasis] approaches to effectively monitor and evaluate the quality and appropriateness of anesthesia care provided by individuals in any department/service in the hospital, including but not necessarily limited to, the ambulatory care, dental, etc., ..." Later, on the same page, they state that, "we believe this should not be used as an excuse to avoid *participating* [italicized for emphasis] in the evaluation of the quality and appropriateness of the use of anesthetic drugs outside the operating room." Further, on page 275, they state that, "as the JCAHO is advocating the active participation of anesthesiologists in monitoring and evaluating anesthetic care in hospital departments outside the operating room, neglecting this responsibility may put the anesthesiologist at risk for litigation problems in the future."

JCAHO standards do *not* require that the director of the organized anesthesia department/service *develop* "approaches to effectively monitor and evaluate . . . etc.," but rather that he or she *participate* in their development. The director is not required to assume responsibility for administration of anesthesia for those over whom he or she has no authority. To clarify the entire issue, the Intent of the standards has been published (2) in the Scoring Guidelines of the 1992 *Accreditation Manual for Hospitals*, Volume II, Surgical and Anesthesia Services chapter, page 7. The following is the exact wording of the scoring guidelines:

> INTENT The director of the organized anesthesia department/service, or a designee(s), directly participates with individuals from all other departments/services in which anesthesia services are provided in the development of mechanisms or processes
>
> - to provide services that are consistent with patient needs and current practice,
> - for monitoring and evaluating anesthesia services, and
> - for establishing guidelines for the safe administration of anesthesia.
>
> These standards do not prevent other directors from assuming responsibility for anesthesia services provided in their department/service. If the director of organized anesthesia service objects to a policy established by an individual department/service director and the disagreement cannot be resolved, it should be brought to the medical staff for resolution through appropriate established channels (for example, the medical staff executive committee).
>
> The director of each department/service in which anesthesia services are provided is responsible for the monitoring and evaluation of the quality of patient care provided in the department/service, consistent with current knowledge of anesthesia practice. The director of the organized anesthesia department/service facilitates and provides consultation on the monitoring and evaluation of the quality of anesthesia services provided in hospital departments/services.

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In Response:

Anesthesiologist's interactions with medical departments outside the operating room are often limited. The intent of our survey and analysis (1) is to call the attention of anesthesiologists to the frequent use of anesthetic drugs by nonanesthesiologists and to point out that as a specialty, we can be an important resource for other medical departments utilizing anesthetic drugs.

We thank Drs. Epstein and Schyve for their interest and comments. We agree that the directors of each department are ultimately responsible for the quality of patient care in their own departments; however, we should not avoid our responsibility in helping with the monitoring and evaluation of the quality of anesthesia outside the realm of our direct control.

Who should know better the use of anesthetic drugs and safety concerns of administering an anesthetic than an anesthesiologist?

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Preemptive Analgesia: An Early Observation

To the Editor:

Ejlersen et al. (1) in a well-designed study have added another valuable piece of information in the evolving field of preemptive analgesia. They did not, however, cite a reference that deserves to be credited as one of the earliest scientific observations in this area. Neill (2) reported in 1978 reduced need for postoperative analgesia in patients after regional anesthesia, compared with the same patients after general anesthesia. Despite this report, interest seems to have remained dormant until the major advances in pain mechanisms of the early 1980s.

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In Response:

We are grateful to Dr. Bourke for drawing our attention to the report by Neill (1), which unfortunately escaped our attention. However, the study by Neill did not address the key question in our paper: whether preincisional infiltration of the surgical wound is more effective in preventing postoperative pain than postincisional infiltration. Rather, Dr. Neill only showed that preincisional plexus block with bupivacaine before general anesthesia significantly increased the time to administration of the first postoperative analgesic compared with general anesthesia alone.

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Colorimetric Carbon Dioxide Detection

To the Editor:

The recent article by Sum Ping et al. (1) reiterates the concern that diagnosis of esophageal intubation using capnography or colorimetric detection may be difficult if CO_2 is present in the stomach (2,3). Their conclusions, however, that the FEF CO_2 detector (now Easy Cap, Nellcor) is not suitable for determining correct placement of the endotracheal tube are not well supported by their data nor those of other investigators. We contend that the article has certain study design features that significantly limit the application of their data to the clinical situation, and, further, we would like to cite several studies that appear to contradict to some degree their results. Readers might be encouraged to peruse the reports of O'Flaherty and Adams (4), Goldberg et al. (5), and Varon et al. (6), which collectively represent 222 patients in which use of the FEF (now Easy Cap) detector was shown to be highly effective.

With regard to the study design in the article by Sum Ping et al. (1), the swine (unknown weights) had 150 mL of carbonated beverage instilled into their stomachs, followed by six normal tidal breaths via an endotracheal tube placed in the esophagus and then had the CO_2 detector connected to the esophagal tube. It appears that no time was allowed to elapse between the instillation of the beverage and the evaluation of the CO_2 detector other than the six breaths. The chances of a rapid engulfment of this volume of carbonated beverage occurring within seconds or even 1 or 2 min before intubation is not likely. Further, the volume of beverage may have been in excess of normal human intake, depending on the weight of the swine. A more appropriate study design would have incorporated timed evaluations of the CO_2 detector for periods up to 1 h after instillation of the beverage. In fact, Heller et al. (7) conducted studies evaluating the same detector in swine 5–10 min after beverage instillation and with cardiorespiratory arrest. They found that after 5 min, carbonated beverages did not result in false color changes in the colorimetric detector. In similar studies evaluating capnography with esophageal intubation after carbonated beverage ingestion in dogs, Garnett et al. (2) found that 40% had no esophageal capnographic record after 10 min and that 60% had average peak CO_2 concentrations of 5.18% ± 2.61%, decreasing to <1% after eight breaths, and in those animals monitored for 20–30 min, the CO_2 concentrations were approximately 0.2% after six breaths. These low levels of CO_2 (~0.2%) did not cause Heller et al. (7) any difficulty with use of the disposable colorimetric detector.

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In Response:

The concerns put forward by Drs. Butler, Leiman, and Katz were (a) limited application of our data owing to the design of our study; and (b) contradiction between our results and those of other studies. Our response follows.

In our study (1), esophageal ventilation was performed soon after the administration of carbonated beverage. We believe that the CO_2 level would have been higher had we waited 10 min, because the time for the CO_2 level to reach a maximum after the instillation of carbonated beverage into the stomach is 10 min, as shown in our previous report (2). This probably explains why Garnett et al. (3) observed a CO_2 level >8% (our highest CO_2 level was only 5.3%) during esophageal ventilation 10 min after the instillation of carbonated beverage. Garnett et al. (3) did not wait 20 and 30 min before performing esophageal ventilation, as implied by Dr. Butler and colleagues. They repeated esophageal ventilation in the same animals at 20 and 30 min without further instillation of carbonated beverage, and the CO_2 levels obtained were predictably lower at 0.90% ± 0.22% and 0.60% ± 0.08%, respectively. We believe that the CO_2 levels would have been higher had the esophageal ventilation been performed for the first time at 20 or 30 min. The real question here should be, how does time affect CO_2 concentration in the stomach after instillation of carbonated beverage? The CO_2 concentration depends on the rate of production and excretion. The CO_2 is released into the stomach from the carbonic acid in the beverage whenever CO_2 concentration in the stomach decreases below that of the carbonic acid until exhaustion of the latter. Excretion of CO_2 from the stomach is by passive absorption through the mucosa into the blood circulating in the capillaries of the stomach until CO_2 concentration in the stomach decreases to the level present in the blood. A larger volume of carbonated beverage ingested will maintain a high CO_2 concentration for a longer duration. In our study, 150 mL of carbonated beverage at 2°C was administered to Yorkshire swine weighing 35–40 kg. How long a can (355 mL) of carbonated beverage will maintain a high CO_2 level in the stomach of a 70-kg person cannot be extrapolated from our study. We wanted to show that high CO_2 level can be obtained during esophageal ventilation in the presence of carbonated beverage in the stomach, a finding that conforms to the results obtained by Garnett et al. (3) and Zbinden and Schüpfen (4).

Heller et al. (5) did not observe any color change in the FEF CO_2 detector (now Easy Cap, Nellcor) during esophageal ventilation in any animal after the instillation of carbonated beverage into the stomach, whereas in our study, there was no color change and no CO_2 obtained only in one of six swine. In the Heller et al. study, two of the four animals died during esophageal ventilation, and CO_2 level was not measured quantitatively. It would be difficult to determine whether the absence of color change was real or subjective. In a previous study (2), we showed that the color-matching process with the FEF CO_2 detector was not always easy, and there was a variation in the color chosen by the different blinded observers, even when the volume and CO_2 concentration of the gas mixture injected through the detector were the same. During cardiopulmonary resuscitation (CPR) of the remaining two animals, the FEF CO_2 detector was not used to monitor tracheal ventilation. The color change corresponding to low CO_2 level obtained with tracheal ventilation during CPR can easily be confused with the color change in the FEF CO_2 detector during esophageal ventilation.

Our results did not contradict those of O'Flaherty and Adams (6) and Goldberg et al. (7), although our conclusions differ. They both conclude that the FEF CO_2 detector is safe and reliable on the basis of successfully identifying esophageal intubation in 19 and 11 instances, respectively. All patients in both studies had normal hemodynamics. When the hemodynamic is compromised, as during CPR, the FEF CO_2 detector is no longer reliable in assessing correct placement of the endotracheal tube, especially in the presence of carbonated beverage in the stomach. Small or no color change in the FEF CO_2 detector can occur with both esophageal and tracheal ventilation during CPR. Contrary to what Dr. Butler and colleagues mentioned, Varon et al. (8) found the FEF CO_2 detector to be reliable in identifying esophageal intubation only after emergency intubation for respiratory distress and not during CPR, a conclusion that concurred with our belief.

We would like to point out a very important principle in the assessment of various monitors. Whether a monitor is assessed as good or bad depends on the criteria one demands of the monitor under the conditions it will be used. The capacity to identify placement of the endotracheal tube rapidly and accurately is paramount under any circumstance, including CPR. If, for example, a monitor has a 95% success rate, one would normally tend to assess the monitor as good; but if that monitor is used as the sole means of correctly assessing position of the endotracheal tube when the vocal cords are not visible and a capnographic monitor is not available, is it good enough?

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Respiratory Obstruction in the Recovery Room

To the Editor:

We wish to describe a case that has not previously been described in the medical literature. The patient was a young, healthy woman who underwent an uneventful vaginal hysterectomy. At the conclusion of the procedure, the patient was transported to the postanesthesia care unit while breathing supplemental oxygen spontaneously via an endotracheal tube. On arrival, she was placed on 100% oxygen mist via T-piece and connected to routine monitors. Shortly after arrival, the patient's face was noted to be flushed, and oxygen saturation decreased to the low 90% range. Physical examination revealed minimal breath sounds, bilateral jugular venous distention, and erythema of the neck and face. No mist was observed to be coming from the expiratory limb of the T-piece. She was rapidly disconnected from the T-piece and breathed from the transport oxygen. Her oxygen saturation immediately increased, and auscultation revealed decreased bilateral breath sounds. A chest radiograph revealed bilateral pneumothoraces that necessitated bilateral chest tube placement. Subcutaneous crepitus was noted from her sternum to her orbits. The chest tubes were removed 3 days later, and the subcutaneous emphysema resolved without complication. Inspection of the T-piece revealed that the plastic wrap had been stretched over one open end of the T-piece, which produced complete obstruction when the expiratory limb was added. The fresh gas flow of 15 L/min increased intrathoracic pressure, impeded venous return, and caused the bilateral pneumothoraces and subcutaneous emphysema.

We propose that to reduce the risk of this recurring, (a) practitioners be aware of the possibility and include it in the differential; (b) respiratory therapists be trained to completely unwrap the T-piece before assembly; and (c) practitioners listen to the chest after connecting any respiratory therapy device and note the presence of expired mist in the expiratory limb.

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A Preliminary Study of the Ultrasound Examination of the Vocal Cords and Larynx

To the Editor:

A noninvasive method for visualizing the vocal cords and larynx would be a useful tool in the management of difficult intubations and as an aid to the diagnosis of vocal cord abnormalities. Therefore, we tested the capability of ultrasound imaging of laryngeal structures to guide endotracheal intubation and to diagnose vocal cord abnormalities noninvasively. Twenty healthy adult volunteers and 10 full-term newborn infants without apparent laryngeal pathology were successfully scanned. As shown in Figure 1, the false vocal cords appeared as paired hypoechoic structures, and the true vocal cords appeared as paired hyperechoic structures. The symmetric abduction/adduction of both the true and false vocal cords was easily observed. Ten adult patients undergoing direct laryngoscopy to evaluate suspected vocal cord lesions were also scanned. In each case, ultrasound scanning demonstrated the presence of vocal cord paralysis seen on direct laryngoscopic examination. Next, the real-time ultrasound image of the vocal cords and larynx was successfully used to guide the endotracheal intubation of an awake, healthy volunteer (Figure 2). However, additional attempts using ultrasound-guided endotracheal intubation in 10 anesthetized patients proved unsuccessful in 8 as a result of difficulty in adequately visualizing the tip of the advancing endotracheal tube. The use of a stylet, foam cuff, or Doppler implanted endotracheal tube did not increase endotracheal tube visualization. The present study demonstrates that high-resolution ultrasonography is capable of producing good quality images of the vocal cords and larynx. Further

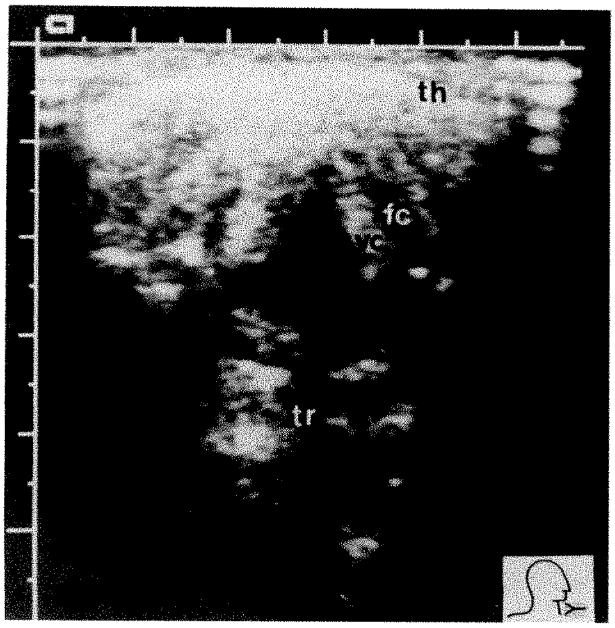

Figure 1. Laryngeal (transverse) sonogram in a healthy female volunteer. fc, false vocal cords; vc, true vocal cords; th, thyroid cartilage; tr, trachea.

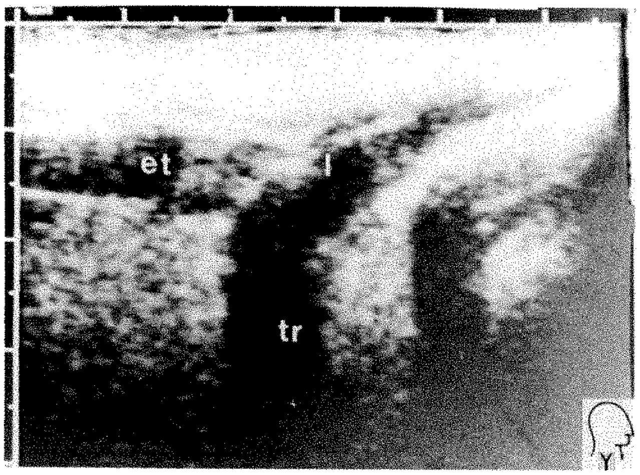

Figure 2. Laryngeal sagittal sonogram in a healthy male volunteer during oral ultrasound-guided endotracheal intubation. et, endotracheal tube; l, laryngeal inlet; tr, trachea.

refinements in this technique are needed before ultrasound will be a clinically useful aid to endotracheal intubation; however, ultrasound may prove to be a clinically useful tool for noninvasive examination of vocal cord movement.

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Morbidity in the Postanesthesia Care Unit

To the Editor:

We agree with Hines et al. (1) that the postanesthesia care unit (PACU) period continues to be a source of morbidity. In a detailed prospective study (unpublished data), we evaluated 389 consecutive patients entering the PACU at a district general hospital. Using a standardized form based on the criteria of Zelcer and Wells (2), the incidence of PACU complications was determined. Each complication was confirmed by one of two anesthetists. Data showed that 32% (n = 124) of patients had 183 complications. Of the 183 complications, the most frequently encountered were pain (22.4%), a pulse oximeter reading <90% (14.8%), and, with agitation, hypotension and nausea, each accounting for 8.7%. According to ASA physical status, the percentages of patients with complications were ASA I 29% (n = 319), ASA II 38% (n = 61), ASA III 50% (n = 10), and ASA IV 100% (n = 3). The majority of patients (92%) recovered from anesthesia within 60 min of arrival in the PACU. The intraoperative complication rate was 14% (n = 55). Only 12 of the 55 patients with intraoperative complications had PACU complications.

We can thus confirm the appreciable morbidity of the PACU period, especially if the complications are deliberately sought. These surveys are of a useful audit of clinical practice. Although our specific findings can only apply to our institution, the general lessons learned can equally apply to other institutions where anesthetics are administered.

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Combined Spinal and Extradural Anesthesia

To the Editor:

We read with interest the letter by Eldor et al. (1) describing the adaptation of the Tuohy needle for use in the combined spinal and extradural technique. Combined spinal and extradural anesthesia has become the technique of choice for most emergency and elective procedures performed under regional anesthesia in our obstetric unit. In fact, over the past 2 yr, we have performed more than 500 elective cesarean sections using this technique without ever having to resort to general anesthesia. This contrasts sharply with the stated incidence of 0.46%–35% failure rate with sole use of spinal anesthesia (2). We normally use a 26- or 27-gauge 120-mm-long spinal needle through a standard 16-gauge Tuohy needle and have encountered no serious complications. We believe that the adaptation of the Tuohy needle suggested in the letter by Dr. Eldor and colleagues is unnecessary and increases the technical difficulty of the procedure. The only theoretical advantage of this needle is that it may prevent the extradural catheter from accidentally passing through the hole made in the dura by the spinal needle. However, since the use of the needle-through-needle technique, first reported by Coates (3) in 1982, there has been no report in the international literature of an extradural catheter breaching the hole made by the spinal needle in the needle-through-needle technique. Combined spinal and extradural anesthesia has become increasingly more popular in our unit because it provides rapidity and density of spinal block, combined with the ability to extend the block and provide postoperative analgesia by use of the extradural catheter. It is also thought to be associated with a lower incidence of postdural puncture headache (4).

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In Response:

In reply to Dr. Patel's letter concerning our combined spinal-epidural needle, newly named the Eldor needle, it is not only an "adaptation of the Tuohy needle," but a completely different concept in regional anesthesia.

I agree with Dr. Patel's description of the benefits of combined spinal-epidural anesthesia versus spinal anesthesia alone (or epidural anesthesia alone, which he did not mention); however, I disagree with him about the advantages or disadvantages of the Eldor needle compared with the needle-through-needle approach that he and his colleagues are using.

Using the Eldor needle, you can place the epidural catheter *before* inserting the spinal needle. In the Eldor needle, there is no risk of producing metallic particles while pushing the spinal needle through the bent-end portion of the Tuohy needle (1). With the Eldor needle, you do not need long spinal needles, which are more prone to fracture. These three advantages of the Eldor needle over the needle-through-needle approach are obvious and make it a superior approach.

I did not mention the danger of an inadvertent epidural catheter protruding to the spinal space through the hole made previously by the spinal needle, which Dr. Patel mentioned in his letter.

The Eldor needle does not "increase the technical difficulty of the procedure"; on the contrary, it decreases it. Perhaps Dr. Patel or one of his colleagues had difficulty placing the epidural catheter after the patient had received the spinal anesthetic injection. The small conduit attached to the side of the epidural needle in the Eldor needle does not create any technical difficulty, and the sensitivity is almost equal that of the original Tuohy needle. You can compare it to a spaceship on top of its missile.

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Securing an Endotracheal Tube in the Presence of Facial Burns or Instability

To the Editor:

Temporarily securing the oral endotracheal tube in a patient with a burned or unstable face can be a difficult challenge. Facial fractures, with or without facial burns; loss of teeth, with or without facial fractures or burns; or a facial burn requiring debridement periorally all often present problems in terms of securing the oral endotracheal tube. The traditional approach has been to wire the endotracheal tube to a stable molar or to secure the tube to the face using standard or umbilical tape. Wire can cause damage to teeth, and tape, either standard or umbilical, is sometimes not optimal from a surgical standpoint nor safe from an anesthetic and patient standpoint. External taping can impede facial debridement, and the blood caused by debridement can loosen the tape, making an extubation or mainstem intubation more likely.

Another useful technique involves placing a heavy braided suture, such as 0 silk, circumferentially around the lingual base of teeth, which have a narrower apex than biting surface (Figure 1). Several knots complete the tie around the buccal surface. Approximately 2 cm above the knot that secures the tie around the tooth another knot is made. The endotracheal tube can then be secured against this knot. This creates a short leash for the endotracheal tube, which is anterior to the tooth, and facilitates visualization of the tube while effectively preventing significant upward and downward movement. Because the surgeon may wish to place his or her gloved finger in the oral cavity to facilitate the debridement, one should not tie around

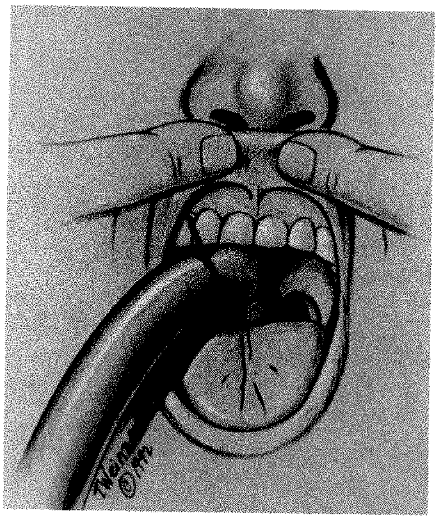

Figure 1. Heavy suture is placed around a tooth and a knot tied. A second knot alone creates a leash for the endotracheal tube.

both upper and lower teeth. The suture can easily be removed when extubation is appropriate by cutting it at the base of the tooth with a scalpel or needle edge.

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Dr. Joseph Eastman Sheehan's Influence on the Introduction of Modern Anesthesia in Spain

To the Editor:

The Irish-born surgeon Joseph Eastman Sheehan (1885–1951) studied and practiced in the United States, achieving worldwide fame in the field of plastic surgery, for which he developed a number of widely adopted techniques. His wide-ranging interests also included cultural, social, and even diplomatic affairs (1). It was nevertheless in a professional and humanitarian capacity that he twice visited Spain.

In 1928, Sheehan came to Spain at the behest of King Alfonso XIII to treat patients suffering from the sequelae of wounds received in the Moroccan war (2). He operated on a number of facial paralysis cases at the Military Hospital of Madrid, was decorated by Alfonso XIII, and made numerous friends in Spanish society.

In 1937, during the Spanish Civil War of 1936–1939, Sheehan returned to Spain when the leader of the insurgent troops, General Franco, invited him to organize a military plastic surgery unit for the many casualties with severe face wounds (3). He was given the rank of honorary colonel and set up his unit at the General Mola Hospital in San Sebastian, behind the northern war front where most of the face wounds were produced. Not content with running the unit, which contributed greatly to the treatment of the wounded, Sheehan also organized training courses in plastic surgery that were attended by numerous military surgeons (4).

Among other problems to be overcome in setting up the plastic surgery unit were the outdated anesthetic practices of Spanish hospitals of the time. The usual procedure in operating theaters was for nurses or medical students to administer ether with the crude Ombredanne inhaler. Because this was totally inadequate for Sheehan's purposes, he sought the collaboration of Robert Macintosh, Professor of Anesthesia at the University of Oxford. Macintosh spent 6 wk in San Sebastian in late 1937 performing anesthesia with endotracheal intubation and in early 1938, was replaced by his colleague Kenneth Boston (5). Thanks to Sheehan's initiative, many Spanish surgeons had the opportunity to witness, and some to become familiar with, anesthetic techniques that were at that time unknown in Spain.

When on leaving Spain in the spring of 1938 Sheehan visited General Franco in Salamanca, he urged him to maintain the plastic surgery unit in service (1). Franco's response was to send the young Spanish military surgeon Sánchez Galindo to the United States to receive instruction, under Sheehan's patronage, in the foremost U.S. surgical clinics, where he learned both surgical techniques and the basics of modern anesthesia. On his return to Spain, he applied his new skills to war casualties; after the war, he continued to practice the anesthetic techniques he had learned in the Military Hospital of Madrid until the mid-1940s, when the first Spanish anesthesiology specialists were trained.

To conclude, we wish to pay tribute to Sheehan's memory for his professional, organizational, and humanitarian efforts in relation to the Moroccan uprising and the Spanish Civil War and for his tangible influence on the modernization of anesthesia in Spain.

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The Element of Experience in Internal Jugular Vein Catheterization

To the Editor:

Hayashi et al. (1) assigned pediatric patients undergoing internal jugular vein catheterization (IJVC) to different operators in an attempt to learn whether experience was a factor that contributed to success or complication. The subject of percutaneous central venous access, both in adult and pediatric patients, has been widely addressed in journals and textbooks since being introduced more than 40 yr ago (2–5). First, the acquisition of this knowledge does not require years of experience or exposure. Second, technical facility (needle manipulation) is not very demanding and requires little practice to reach a reasonable level of proficiency. Third, the very act of "supervising" largely confers the knowledge of the supervisor on the operator. It is for these reasons that "experience" could not have had an effect in their study. Published in abstract form, we concluded in 1979 that the teaching of IJVC could be accomplished without significantly compromising the result (success/complication) in a nearly identical study with essentially the same results (6). This might have been a more appropriate conclusion for Hayashi et al. (1) on the basis of their study design.

More knowledge is required rather than practice of the technical component to increase success and to avoid puncture of the carotid artery. The success and carotid puncture rates are essentially predictable with the knowledge of the frequency with which the carotid artery and internal jugular vein bear a consistent relationship to the more superficial anatomic landmarks used. Denys and Uretsky (7) have provided data from ultrasound assessment in adults and found vascular position divergent from surface landmarks leading to failure or carotid puncture, or both, at a frequency of approximately 8%. Utilization of this knowledge (ultrasound visualization of exact rather than assumed location) during needle placement permits nearly 100% success and, with attention to detail, should eliminate carotid puncture (8).

It is logical to apply the ultrasound technology found to be successful in adults, because it appears that no significant improvement has occurred in IJVC in pediatric patients in more than 10 yr. It is likely that success rates and reduced complications will result in making IJVC more useful, safer, and more widely accepted. This would help to achieve one of the difficult goals of the clinician-educator: providing knowledge and skill for the student without compromising the result for the patient.

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Dextran Absorption During Hysteroscopy With Hyskon, and the Biodegradation of Dextran

To the Editor:

In their article on dextran serum levels during hysteroscopic procedures with Hyskon, Mangar et al. (1) make an important contribution to our understanding of some adverse reactions observed during these procedures. Most of the side effects of Hyskon appear to be due to a sudden increase in circulating blood volume. Before this study, little was known of the extent to which Hyskon would pass into the intravascular compartment during various types of hysteroscopic procedures. This study has clearly demonstrated that at least one-third of the volume of Hyskon used can be fairly rapidly absorbed in connection with hysteroscopic ablation of the endometrium. It should be noted that the amounts of Hyskon used by the authors are within the recommended limits and that the procedures lasted <30 min. In contrast, most reports of adverse reactions have involved volumes exceeding the recommended limits; in some reports, >1000 mL has been used during long-lasting hysteroscopic surgery (2,3). In the abstract preceding the report, it is stated that the authors have correlated the amount of Hyskon used with instillation pressures, but the influence of pressure during injection of Hyskon is not clear from this article, because there seems to be a mistake with regard to the figures given on page 188; comparison with Figure 1 shows that the data reported represent the correlation between *dose* of Hyskon and serum levels. However, on page 189, the authors make a number of erroneous statements with regard to the biodegradation of Hyskon, claiming dextran 40 to be a product during this process and attributing this to a number of negative effects, such as elevations in blood glucose levels, errors in blood cross-matching, decreased platelet adhesiveness, renal failure, and decreased plasma levels of fibrinogen and of Factors V, VIII, and IX. Hyskon is composed of 32% dextran 70 and 10% glucose. Both dextran 70 and dextran 40 are mainly excreted in the urine in unaltered form, 50% and 70%, respectively, being excreted in this way within 24 h after a single dose. The larger molecules of either of these dextran fractions will gradually be absorbed into the reticuloendothelial system and degraded by the enzyme dextranase and subsequently metabolized to carbon dioxide and water, a process that will be completed in 2–3 wk. It is thus impossible for the "biodegradation" of dextran 70 to result in the patient accumulating dextran 40, which is composed of much lower molecular dextran fractions that are more easily excreted by the kidneys. Further, none of these dextran fractions will have a measurable influence on blood glucose levels, and the amount of glucose being supplied as such in the Hyskon solution would be small in the study patients, at most 20 g. Blood cross-matching is not influenced by modern dextrans to a degree that poses any problems in clinical practice, the effect of higher levels of dextran being only that of slightly increased rouleaux formation of the erythrocytes. Renal failure has on very rare occasions been observed after dextran 40 when high doses have been administered as the sole infusion to dehydrated patients but has not been reported after dextran 70. The effects of dextrans on platelet adhesiveness are specific, whereas the lowered levels of fibrinogen and coagulation factors appear to be related to hemodilution alone, according to a recent study (4). None of these effects can be labeled side effects, because they form at least part of the basis for the thromboprophylactic effect of dextrans, which is one of the main indications for the use of these agents.

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In Response:

I would like to thank Dr. Ljungström for acknowledging our contribution to the understanding of some adverse reactions observed during hysteroscopy with Hyskon. As he correctly indicated, Figure 1 correlated the dose of Hyskon with serum levels. (The preceding sentence should have read, "A significant correlation between dose and serum levels. . . .") Because of the limitations of the hysteroscope, we were able to intermittently measure intrauterine pressures (10–160 mm Hg) when the surgical procedure could be halted. The Hyskon injection pressures were measured throughout the procedure (0.5–3.9 atm). Hence, correlating instillation pressure with doses was impossible, because intrauterine pressure could not be measured continuously.

Both dextran 40 and dextran 70 are polymers of glucose. Dextran 40 has 90% of its polymers with a molecular mass between 10,000 and 80,000 daltons. Dextran 70 contains polymers with molecular mass between 25,000 and 125,000 daltons (1,2). My hypothesis, which was not clearly stated in the article, was that dextran 40 possibly resulted from the disintegration of dextran 70. I agree with the reported route of elimination (3), as described by Dr. Ljungström.

We stated the adverse effects of dextran 40, which are clearly documented in the literature (1–11), and have seen no reference from Dr. Ljungström to support the contrary viewpoint. For example, we reported a "factitious" elevation in blood glucose because the blood glucose analysis required high acid hydrolysis concentration that may hydrolyze dextran to glucose. Dextran also produces a turbidity that interferes with orthotoluidine glucose measurements, resulting in a "factitious" elevation in blood glucose.

These "erroneous" statements, as described by Dr. Ljungström are in fact adverse reactions to dextran 40, and I was not implicating the reaction to dextran 70. Data and Nies (3) described seven paradoxes of dextran 40. These authors advise against using this agent so long as alternative therapy of equal efficacy and fewer side effects is available. One might question the use of dextran for thromboprophylaxis when other safe alternatives to dextran are available.

Bleeding diathesis exists after intravascular absorption, as demonstrated from published reports (12–18). A recent case report (18) describes a patient with extensive bleeding after 700 mL of intrauterine Hyskon, necessitating hysterectomy. Clearly, this is not only a dilutional effect (19), but a bleeding problem resembling a disseminated intravascular coagulation profile, possibly attributed to the effects of dextran 70. In most of the other published reports (12–17), the same bleeding pattern was seen.

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Angioedema of the Tongue—Cause?

To the Editor:

A case report by Kharasch (1) discusses a 67-yr-old patient who developed angioedema of the anterior one-half of the tongue following extubation of the trachea after release of a Dupuytren's contracture under general endotracheal anesthesia. The author associates the angioedema with the initiation of enalapril, an angiotensin-converting enzyme (ACE) inhibitor, 10 days before surgery. Other causes of the angioedema are dismissed, even though enalapril is not clearly shown to be the cause. The possibility of hereditary angioedema, caused by deficiency of C1 inhibitor (C1 INH), is dismissed because the patient had no previous episodes of angioedema.

Angioedema after even mild trauma to tissue should always raise concern about C1 INH deficiency. Although patients with this hereditary disorder often present earlier in life, there are reports of patients presenting as late as the sixth decade of life (2–4). The average time from onset of symptoms until the diagnosis is made is 21 yr (2). In addition, acquired forms of C1 INH deficiency exist that typically present after the fourth decade (5). Acquired deficiency may be associated with benign or malignant B-cell proliferative states and essential cryoglobulinemia or may result from the idiopathic production of an autoantibody directed against the active site of the C1 INH molecule (6).

A rapid screening test for C1 INH deficiency is the C4 level. A low level suggests the diagnosis of C1 INH deficiency and may be followed with measurement of C1 INH antigenic levels and an assessment of its functional activity. Low C1 and C1q levels identify the acquired disease; C1 levels are normal in the hereditary form.

Recognition of C1 INH deficiency is paramount because treatment is drastically different in these patients than in those with angioedema that is allergic or idiopathic in origin. Patients with C1 INH deficiency generally do not respond to therapy with epinephrine, antihistamines, or glucocorticoids. Management of acute angioedema due to deficiency of C1 INH is difficult. Fresh-frozen plasma contains C1 INH but also contains the substrates for the enzyme, uncleaved C2 and C4. Theoretically, this may serve to fuel complement activation, and in practice, there are reports of patients worsening after administration of fresh-frozen plasma. In addition, administration of blood products carries the risk of possible infectious complications. Replacement therapy with purified C1 INH is available in Europe but not currently in this country.

Appropriate management of a patient with C1 INH deficiency involves preoperative recognition of the condition. Prophylaxis with anabolic steroids, such as oral danazol (600 mg daily) or stanozolol (6 mg four times a day) should be initiated 5–10 days before surgery (6). These attenuated androgens apparently enhance C1 INH synthesis. Thus, androgens provide effective prophylaxis without the increased risk of alternative preventative therapy with fresh-frozen plasma or ε-aminocaproic acid.

Certainly this patient may have had angioedema related to recent institution of enalapril or some other cause; however, deficiency of C1 INH, hereditary or acquired, has not been excluded.

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In Response:

The case of ACE-inhibitor angioedema of the airway was reported to afford an awareness of this syndrome and its appropriate management among those potentially called on to secure the compromised airway of such afflicted patients. Drs. Maves and Weiler have expanded the dialogue to include hereditary angioedema. They describe eloquently the causes, proper evaluation, and appropriate management of C1 inhibitor deficiency.

These authors question whether a C1 inhibitor deficiency might have been the cause of the angioedema described in the case report. Two points deserve mention. First, C1 inhibitor deficiency is dismissed not only because the patient had had no previous episodes of angioedema during his 67 yr (1), but because he did have a normal C4 level (26 mg/dL; normal range 12–40 mg/dL) and normal C1 inhibitor activity (activity >95%; normal defined as >67%). Second, ACE-inhibitor airway angioedema is potentially life threatening and may recur even after apparent resolution (2,3). Laboratory evaluation of C1 inhibitor deficiency may take several days. Although it is certainly important to eventually rule out a C1 inhibitor deficiency, definitive therapeutic and preventative measures in a patient with suspected ACE-inhibitor angioedema should not await laboratory exclusion of other possible causes. The ACE inhibitors should be considered the cause of angioedema whenever it occurs in patients taking these drugs (4). The drug should be immediately discontinued, preferably by or in consultation with the prescribing physician.

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Book Reviews

Contemporary Issues in Chronic Pain Management

W. C. V. Parris, ed. Boston: Kluwer Academic Publishers, 1991, 311 pp, $115.00.

Pain management is a rapidly emerging discipline. In the sphere of acute pain, new pharmacologic approaches, drug delivery systems, as well as organizations within the hospital community to deliver acute pain relief, have evolved only in the last few years. In the sphere of chronic pain, despite the general consensus on the efficacy of long-term opiate management of cancer pain, the rate of progress has been something less than a blur. Thorny problems continue to confront the clinician. Nevertheless, in certain areas, there is cause for quiet excitement.

Contemporary Issues in Chronic Pain Management seeks to give an honest appraisal of the state-of-the-art, candidly listing the assets and liabilities of this developing, and uniquely human, enterprise. New developments are held up as pearls of opportunity for the future (an asset), while much remains to be discovered (a liability). Despite the unevenness of its multiauthored prose, this text succeeds in convincing the reader that the assets well outweigh the liabilities, and that the enterprise is running well in the black.

The volume begins by taking a historical tack, examining whence pain management has come, that we may see wither it is going. In so doing, it confronts the highly charged political issues of: Who will lead? Who will govern? Who will be the standard-bearer, and more importantly, who will certify people for the practice of pain management? Will it be the American Pain Society, the American Academy of Pain Medicine, or will it be some other organization? I am sure that many readers eagerly wait to see what happens once the dust settles.

The chapter on how ethnicity, culture, and religion affect chronic pain, although perhaps not politically correct, was fascinating, entertaining, and fun reading. The myriad ways in which a person suffers when they are hurting probably has a great deal to do with who their parents were and what sort of society they came of age in. For the future, we can anticipate more revealing studies of this subject, whose surface has been barely scratched by researchers.

The fifth chapter by Harrison, titled "Endorphins and Narcotic Drugs: Pain Control Paradigms vs. Legal Realities" raises some very thought-provoking issues regarding the use of narcotics in the management of chronic pain. For example, at present, statutes do not discriminate between people who use narcotics to relieve their pain and people who abuse them for fun and profit, taring both groups with the broad brush of "Drug Addicted Person." We now know that our own bodies produce endogenous opiates (endorphins) that have the same effect upon the nervous system as the legally controlled group of substances called "narcotics," about which much criminal law is written. Given that, does it really make sense to stigmatize people with severe cancer pain, who use them for pain relief, as "drug-addicted persons"? Obviously not. The author suggests that our pharmacologic science has leapfrogged ahead of the law, developmentally speaking, and that now it is time for the law to play catch-up.

One of the causes for quiet excitement given excellent treatment is our evolving understanding of the pharmacology of substance P and related algesic substances acting at the level of the peripheral pain receptor, and the effectiveness of capsaicin, an extract of red pepper, at this level in the pain pathway. As author Szolcsanyi puts it, "There is a 'painfully' absent chapter in pharmacological textbooks, which could be entitled: 'Drugs acting on sensory neurons,' or 'Sensory neuron-blocking analgesics.'" In all, three authors speak about the substance P story, marshalling the evidence for its existence and its importance.

The editor offers up the interesting speculation that levels of substance P (as well as other neuropeptides) in different fluid compartments, such as blood, CSF, or even saliva, may serve as a correlate of, or biological marker for, chronic pain. If this is the case, then it follows that by monitoring levels of substance P, we can compare the effectiveness of old and new modalities of chronic pain therapy in an objective way. In an era of ascending cost-consciousness, such studies could carry enormous weight. In any event, it seems reasonable to think that the gap in our pharmacology textbooks alluded to by Szolcsanyi will be filled in the near future.

A chapter on nerve block therapy in chronic pain management by the editor was quite comprehensive and included pearls from the author's own practice about how to avoid pneumothorax in suprascapular nerve block. Neurolytic blocks for chronic cancer pain are mentioned in passing, and there is no mention of new developments such as superior hypogastric plexus neurolytic blocks, or ganglion impar blocks for the relief of pelvic and rectal pain, respectively. The natural history and treatment of reflex sympathetic dystrophy is well described.

A useful and interesting chapter on the history and state-of-the-art of thermography is provided. A final chapter on low-level laser biomodulation for chronic pain management contained the clearest explanation I have yet seen in the medical literature of how lasers function. The chapter rapidly became arcane and opaque when trying to show how this "solution in search of a problem" can be of help to the chronic patient.

In all, the editor succeeds in tying together many diverse subjects with a common thread. I would recommend this

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book for people already involved in the practice of pain management, and for people who are well acquainted with pain management literature.

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Anesthesia for Ophthalmic and Otolaryngologic Surgery

Kathryn McGoldrick, ed. Philadelphia: W.B. Saunders, 1992, 318 pp, $50.00.

Although there are many books available on subspecialty anesthetic practice, there is no current, comprehensive text dealing exclusively with anesthesia for otolaryngologic and ophthalmic surgery. As noted in the foreword to the book, this is remarkable, considering that anesthesia for ENT and eye procedures involve many challenges, including that of the shared airway. Fortunately, Kathryn McGoldrick and her colleagues have filled this void. *Anesthesia for Ophthalmic and Otolaryngologic Surgery* is a comprehensive, well-written text on the subject.

This reference work comprises 22 chapters, 16 of which were written or cowritten by the editor, Dr. McGoldrick. Consequently, it is cohesive and not overly repetitive. There is deliberate emphasis on anesthesia for pediatric and geriatric patients, as well as outpatients.

The book is divided into two sections. The first has 12 chapters devoted to anesthesia for otolaryngologic surgery and covers a wide range of topics including difficult intubations, pediatric airway emergencies, anesthesia for outpatient procedures, and laser surgery of the airway. These chapters are notable for their depth and clarity. For example, the chapter on anesthesia for elective otolaryngologic surgery includes a thorough discussion of the pathophysiology of patients, such as those with cystic fibrosis, who commonly present for ENT procedures. The chapter on anesthesia for airway emergencies discusses ordinary problems, such as the bleeding tonsil, as well as rare dilemmas like diphtheria.

As a reflection of the quality of the text and the clinical experience of the authors, facts accumulated from numerous investigations are usually synthesized into a cohesive set of conclusions; however, although most of the facts are supported with a substantial number of references, this is not consistently the case and may be improved upon in subsequent editions. There is an element of "cookbook" style in several of the chapters, but usually the "recipes" are guides and follow a scholarly discussion of the competing issues of particularly difficult clinical problems (epiglottis, open globe/full-stomach, etc.). The authors go to great lengths to emphasize that there may be several correct methods of patient management in some situations.

The second section deals primarily with anesthesia for eye surgery. It discusses many topics that anesthesiologists will be thankful to find consolidated in one text. These include anatomy and physiology of the eye, anesthetics and intraocular pressure, pediatric ophthalmologic surgery, ocular pathology and systemic diseases, and anesthetic ramifications of ophthalmic drugs. This section also displays substantial depth and is quite comprehensive. For example, the chapter on ocular pathology and systemic diseases engages in a scholarly review of congenital and metabolic disorders associated with ocular disease. The detailed information on 18 syndromes is consolidated in concise tables for easy reference when these patients (mainly children) present for eye surgery, often on an ambulatory basis.

In summary, Dr. McGoldrick and her colleagues have provided us with a tremendously useful resource. This book is comprehensive, well-written, and scholarly. At $50 it is an excellent value. It is very highly recommended for anesthesia libraries or for the personal collection of anesthesiologists who care for patients undergoing otolaryngologic or ophthalmic surgery.

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Mechanisms of Anesthetic Action in Skeletal, Cardiac and Smooth Muscle. Volume 301 in Experimental Medicine and Biology Series.

Thomas J. J. Blanck and David M. Wheeler, eds. New York: Plenum Press, 1991, 310 pp, $79.50.

This book presents the results of a symposium held in 1990, the purpose of which was to simultaneously gather at Johns Hopkins University School of Medicine many of the people currently working in areas related to the pharmacodynamics of the volatile anesthetics in the three major categories of muscle. Because many of the contributors are recognized experts in their respective fields, the product of their collective presentations represents not only a display of the good science typical of these individuals, but also an education in the modern physiologic and biochemical techniques applied to this topic. Furthermore, the new data presented are built on very recent advances already made in the cell biology of each muscle type (e.g., malignant hyperthermia for skeletal muscle, receptor biology for cardiac muscle, and the interaction of the vascular endothelium with vascular smooth muscle). Recognition that these fields are not mutually independent is provided in a chapter dealing with coronary vascular smooth muscle reactivity in situ; that is, coronary blood vessels situated in their natural physical environment in close proximity to, and undoubtedly affected by, cardiac muscle. One is struck by the inventive experimental approaches used to separate the effects of anesthetics on each muscle type in such a preparation and by the relatively close agreement shown using widely diverse experimental systems when applied to selected hypotheses. Lest one be comforted by the prospect of unanimity of expert opinion with regard to the behavior of muscle under anesthesia, however, the book makes clear that there is still serious disagreement concerning fundamental mechanisms at work in this broad and active field.

The first section of the book addresses the effects of anesthetics on skeletal muscle and emphasizes recent advances in the cell biology of malignant hyperthermia (MH). Early in the section, some basic membrane functional abnormalities of MH are discussed, specifically with regard to mitochondria, sarcoplasmic reticulum (SR), and the sarcolemma. Attention is given to recent work supporting a role of abnormal lipid metabolism as a basis for MH; however, experiments with cyclooxygenase inhibitors and lipoxygenase inhibitors have suggested no role for prostaglandins, leukotrienes, or thromboxanes in the abnormal sodium channel function in cultured human MH skeletal muscle cells, as determined by measurements of inward tetrodotoxin-inhibitable sodium currents. Rather, the effects of unsaturated fatty acids on lowering the threshold for calcium-induced release of calcium accumulated by the isolated heavy subfraction of the SR from MH skeletal muscle are emphasized. This threshold, found to be lower in the presence of halothane, is the centerpost of a proposed mechanism favored by some to explain MH. The fact that this curious effect of halothane and other anesthetic gases appears only in genetically susceptible individuals is attributed by these investigators to the presence of a recently discovered genetic abnormality of the calcium release channel of the SR in the Pietrain strain of pig, an MH-susceptible strain used in some laboratories investigating the molecular and cell biology of MH. However, the link between halothane sensitivity and the apparent substitution of a single amino acid in the primary sequence of the calcium release channel protein seems too easily made. These proponents point to an altered binding of the plant alkaloid, ryanodine, to Pietrain-derived SR calcium release channel compared with that of their normal Yorkshire porcine counterparts as direct evidence for a difference in functional behavior between the two proteins. Chapter 6 of the book describes the same ryanodine experiments in normal and susceptible individuals of the same strain of pig (Yorkshire X Duroc cross) and shows essentially identical binding characteristics between the normal and MH conditions. The conclusion seems to be that the previously discovered difference in ryanodine binding was a strain-specific effect rather than a disease-specific effect and that, at least in pigs, not all cases of MH susceptibility are necessarily due to a primary abnormality in the calcium release channel. (It is virtually certain, from genetic linkage studies, that the same is also true for human beings.)

The next section of the book, which covers the effects of anesthetics on cardiac muscle, begins with one of the most revealing chapters in the book, which attempts to bridge the gap between the increased contractility in skeletal muscle and decreased inotropism in cardiac muscle caused by volatile anesthetics. The chapter does so by relating these two opposite tissue effects to the common response of both types of SR to halothane, which is an increased calcium efflux while not affecting the calcium uptake mechanism at clinical concentrations. In skeletal muscle, in which the activating calcium cycles almost exclusively internally throughout the muscle twitch, enhancement of twitch tension is the expected result of halothane exposure. In the smaller cardiac myocyte, however, some activating calcium, after release from the SR during systole, may more likely be rapidly extruded from the cell via the surface membrane calcium pump or facilitated exchange with extracellular sodium ion. This would leave a decreasing fraction of the calcium released by the SR on physiologic activation to be reaccumulated by the SR during diastole over the several beats after the initial exposure. The result of less calcium uptake by the SR is that less is released during subsequent systoles, hence, the negative inotropic effect of halothane. Although this explanation ignores effects of anesthetics on "upstream" calcium flux across the sarcolemma as well as effects on "downstream" calcium binding sensitivity of troponin, these issues are elegantly treated in subsequent chapters in this section that show the delicacy and complexity of the interaction of anesthetics with the heart.

The final section of the book discusses vascular smooth muscle responses to anesthetics. Here, a complicating factor must be considered, that of the vascular endothelium, which produces the recently popularized nitric oxide, a component of the endothelial-derived relaxing factor, or EDRF, as a possible target of anesthetic modification of vascular smooth muscle tone. Therefore, as in cardiac muscle, anesthetic effects on all components of excitation-contraction coupling must be considered, but additional attention must be paid to anesthetic-induced alterations in the function of the nearby vascular endothelium. Accordingly, this section of the book is the most complex and difficult to follow of the three. One finds agent-dependent effects on smooth muscle tone that may or may not change after removal of the endothelium, and one finds effects dependent on the particular vascular bed under study. Finally, whether vascular smooth muscle relaxation or contraction is observed may also depend on the concentration of anesthetic applied and the degree of preactivation produced by added vasocontrictor before addition of anesthetic to maximize possible relaxing effects of the latter. What emerges from the plethora of data and discussion is that there has yet to be proposed a unifying concept to explain the apparently contradictory results in this arena. This may not be surprising, because the apparently universal observation of diminished calcium influx into cells caused by anesthetics might theoretically cause a direct relaxation of vascular smooth muscle as well as decrease the calcium-dependent production of endothelial-derived relaxing factor by endothelial cells, with an experimentally unpredictable overall result on vascular tone.

Finally, on pondering the various methodologies described in the book, one can only be impressed at the wide range of experimental approaches used in this important problem and cannot help but become better educated by reading about them. Although the book is complex and written at a relatively high level for the practicing clinician without special training in the relevant experimental techniques, the reader emerges from the exercise as a more sophisticated critic of the science behind the practice of clinical anesthesia.

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Handbook of Mechanical Ventilatory Support

A. Perel and M. C. Stock, eds. Baltimore: Williams & Wilkins, 1992, 308 pp, $35.00.

An English professor of mine once advised his students that the key to effective writing was, "Know what you want to say and say it." That is exactly what this book does. This primer discusses the physiology and practical aspects of various types of mechanical ventilation in the critically ill. The chapters, for the most part, are concise, direct, and well written by experts with both knowledge and experience in critical care medicine.

The book is divided into three sections. The first section discusses the physiology of mechanical ventilation in various organ systems. These chapters are clinically helpful, and one can imagine a house officer reading them at 2 AM. One exception in the practical bent of the handbook is the pulmonary section, which includes an extensive discussion of experimental animal models of lung injury.

The second section covers the spectrum of ventilatory modes. This section is an excellent resource in that it describes all the major ventilatory modes that are available today, with practical tips on how to use the equipment that is currently available. This information will assist the clinician trained in an earlier era as well as the house officer in deciding among the increasing options for ventilatory support.

The third section applies the principles and mechanical techniques of ventilatory support to specific disease states, such as acute lung injury, COPD, asthma, trauma, and weaning techniques. The last chapter is a summation of the various ventilatory modes contrasting the risks and benefits of each one.

Overall, this book is informative and easy to read, and abbreviations and repetition are avoided. The diagrams, flow charts, and tables throughout the chapters add greatly to the book's usefulness. As an inexpensive, portable handbook, it is a "must buy" for the experimental clinician as well as the house officer on an intensive care unit rotation.

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Clinical Anesthesiology

C. E. Morgan and M. S. Mikhail. East Norwalk, Connecticut: Appleton & Lange, 1992, 747 pp, $39.95

Current anesthesia texts can be divided into three categories: the comprehensive, extensively referenced, authoritative textbook (e.g., Miller, Barash), the introductory textbook (e.g., Dripps/Eckenhoff/Vandam), and the handbook (e.g., MGH, baby Barash). Each of the three types addresses a specific audience and fulfills a specific need. *Clinical Anesthesiology* contains features of all three types. Although paperbound, it is a full-size book that is significantly more comprehensive than typical handbooks and introductory texts. The book covers five sections: anesthesia equipment and monitors; clinical pharmacology; regional anesthesia and pain management; physiology, pathophysiology, and anesthetic management (of specific organ systems, disease states, and procedures); and special problems. The two authors (responsible for 45 of the 48 chapters) write in a clear, straightforward style that is frequently supplemented by illustrations and tables. Each chapter is followed by a case discussion. Although this format could have reinforced important concepts, I frequently found that the case discussion involved core information that should have been directly included in the chapter (e.g., the difficult airway) or information that was relatively esoteric.

In the preface, the authors state that the book is written "primarily for newcomers to the specialty"; however, with over 700 pages of fact-filled text, this book cannot be read during a medical school clerkship or in the beginning weeks of anesthesia training. Thus, this book does not replace the standard introductory texts and handbooks. At the other extreme, the book does not contain the detailed, referenced information (particularly in the subspecialties) needed during the full anesthesia residency and clinical practice. In many respects, the book contains the full knowledge base expected of a resident midway through his anesthesia training. The modest price, size, and weight suggest that this would be an excellent book for residents to use during their first two years.

The text has a significant number of typographical errors that may mislead the reader. For example, the equation for calculating mitral valve flow (page 325) uses diastolic filling pressure rather than diastolic filling period. Table 4-2, describing anesthesia apparatus checkout recommendation, states "20 cm N_2O" rather than "20 cm H_2O." These errors should have been found with careful proofreading.

In summary, *Clinical Anesthesiology* is more comprehensive than the introductory textbooks and handbooks but more readable than the authoritative textbooks. I recommend it for those residents and clinicians who will find such a book to be valuable.

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Books Received

Receipt of the books listed below is acknowledged. Selected books from this list will be reviewed in future issues of the Journal.

The Journal solicits reviews of new books from its readers. If you wish to submit a review, before proceeding please send a letter of intent, identifying the book in question, to Dr. Norig Ellison, Department of Anesthesia, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104. The Journal reserves the right of final decision on publication.

Delooz HH, ed. *Emergency Medicine and the Anaesthetist.* Volume 6, No. 1 in Bailliere's Clinical Anesthesiology Series. London: Bailliere Tindall, 1992, 212 pp, $27.50, ISBN 0-7020-1616-0.

Sinatra RS, Hord AH, Ginsberg B, Preble LM, eds. *Acute Pain. Mechanisms & Management*, St. Louis: Mosby Year Book, 1992, 636 pp, $74.00, ISBN 0-8016-4677-4.

A Guide for Authors

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☐ Technical communications, of 1500 to 2000 words, describe instrumentation and analytic techniques.

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2. *Personal author(s) of books and monographs*
   Eisen HN. Immunology: an introduction to molecular and cellular principles of the immune response. 5th ed. New York: Harper and Row, 1974.
3. *Chapter in a book*
   Weinstein L, Swartz NM. Pathogenic properties of invading microorganisms. In: Sodeman WA Jr, Sodeman WA, eds. Pathologic physiology: mechanisms of disease. Philadelphia: WB Saunders, 1974:457–72.

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2. **American Medical Association. Manual of style. 8th ed. Baltimore, Maryland: Williams & Wilkins, 1989.**

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701E/L

ILLINOIS: ANESTHESIOLOGIST
To join congenial group of MDs/CRNAs expanding to provide anesthesia coverage for only hospital in city since recent merger. No open heart or neurosurgery. Environment conducive to family living, variety of schools, recreation. Good opportunity with stable future. City located in east central Illinois with population of approximately 40,000 (35-mile radius service area with 126,126 population). Within driving distance of Chicago and Indianapolis. Please send CV to Box 887D/L.

887D/L

CARDIOVASCULAR FELLOWSHIP OPPORTUNITY
The Department of Anesthesiology and Critical Care Medicine at the University of New Mexico School of Medicine has openings at the CA-4 level for advanced training in cardiovascular anesthesiology. The fellowship is a 2-year comprehensive program designed to train the fellow for a career in cardiovascular anesthesiology. Research in cardiovascular physiology and anesthesia, provision of clinical care for complex adult and pediatric cases, participation in conference, and teaching responsibilities are part of the fellowship experience. Interested individuals should send CV or contact Jorge A. Estrin, MD, PhD, Professor and Chairman, Department of Anesthesiology, University of New Mexico School of Medicine, Albuquerque, NM 83131-5216, (505) 272-2610, FAX (505) 277-1300. The University of New Mexico is an Equal Opportunity/Affirmative Action Employer.

912F/L

THE UNIVERSITY OF NEW MEXICO
Department of Anesthesiology and Critical Care Medicine has immediate faculty positions at the Instructor, Assistant Professor, Associate Professor, and Professor levels for candidates with experience in cardiac, obstetric, neurosurgical, and pediatric anesthesia and critical care medicine. Responsibilities include the teaching of medical students and residents and the provision of clinical care in a busy tertiary referral center. Opportunities to pursue research interests will be provided. It is expected that candidates who apply for CCM positions will have or be eligible for subspecialty certification. Qualified candidates should send CV or contact Jorge A. Estrin, MD, PhD, Professor and Chairman, Department of Anesthesiology, University of New Mexico School of Medicine, Albuquerque, NM 87131-5216, (505) 272-2610, FAX (505) 277-1300. The University of New Mexico is an Equal Opportunity/Affirmative Action Employer.

913F/L

Immediate opening for a BC/BE anesthesiologist to join six MD anesthesiologists in a fee-for-service practice in a 350-bed hospital in a retirement community in Sun City, Arizona. No OB, open heart, trauma, or pediatrics. Send replies to Box 923GHIJ.

923GHIJ

CALIFORNIA
University of California, Irvine: Openings for faculty positions in the Department of Anesthesiology. (1) Assistant or associate professor level in the in-residence series. Responsibilities include teaching and research. (2) Clinical instructor and assistant professor level in the clinical series. Responsibilities include teaching and clinical service. Participation in research is highly desirable but not mandatory

Rank and pay commensurate with skills and experience. Faculty will serve at both a tertiary-care university hospital and a VA Medical Center. Candidates must be ABA certified, or in the examination process, and be eligible for a California state license. An Affirmative Action, Equal Opportunity Employer. Address correspondence with references and curriculum vitae to Steven J. Barker, PhD, MD, Chair, Department of Anesthesiology, University of California, Irvine Medical Center, 101 City Drive South, Route 81A, Orange, CA 92668.

930G/L

LOUISIANA STATE UNIVERSITY MEDICAL CENTER—SHREVEPORT
Faculty positions available for board certified/eligible anesthesiologists. Duties include patient care, resident and student teaching, supervision of CRNAs, research, and administrative responsibilities. Faculty rank and salary commensurate with experience. Please send curriculum vitae and names of three references to D. Richard Davis, II, MD, Associate Professor and Chairman, Department of Anesthesiology, LSU Medical Center—Shreveport, 1501 Kings Highway, Shreveport, LA 71130-3932. We are an Equal Opportunity/Affirmative Action Employer.

931G/L

TENNESSEE
Expanding department requires additional anesthesiologists. Full-time positions available at levels of instructor to associate professor with emphasis on teaching, patient care, and clinical research. Prerequisites: (1) meet Tennessee license requirements; (2) ABA diplomat or eligible for ABA examination. All subspecialties needed. Excellent opportunity for anesthesiologists who want an ideal mix of private practice with teaching and clinical research. Send curric-

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CLASSIFIED ADS

Anesthesia & Analgesia makes available classified advertising space for those interested in obtaining positions or wishing to announce meetings, postgraduate courses, or other pertinent events. We require that all advertisements be relevant to the practice of anesthesia and analgesia, and we reserve the right to refuse advertisements that are not relevant.

Specifications. Ads should be typewritten on letterhead stationery; the text should be double-spaced, with the title or key phrase typed in capital letters. Enclose two photocopies with each ad. Display space (minimum ¼ page) is available through Pharmaceutical Media, Inc., 440 Park Avenue South, 14th floor, New York, NY 10016, telephone: (212) 685-5010, FAX: (212) 685-6126.

Rates. Ads cost $1.50 per word per insertion, with a minimum of 20 words. Abbreviations, dates, initials, post office box numbers, telephone numbers, years, and zip codes are considered one word each. There is an additional fee of $18.00 per insertion for box number ads.*

Payment. Full payment or institutional purchase order must accompany the copy for each ad. Ads received without a check or purchase order will be returned. (Make checks payable to Elsevier Science Publishing Company, Inc.)

Deadline. Copy must be received 7 weeks before publication date (i.e., by January 1 for the March issue); multiple-insertion ads are welcome. Ads may run up to 6 months per purchase order/payment. Please specify in which issue(s) your advertisement is to appear.

Send all ad copy, payments, and correspondence to: *Anesthesia & Analgesia*, Classified Ads, Desk Editorial, Elsevier Science Publishing Co., Inc., 655 Avenue of the Americas, New York, NY 10010.

*When responding to a box number ad, include the box number on all correspondence.

ulum vitae, bibliography, and the names and addresses of three references to John Zanella, Jr, MD, PhD, Professor and Chairman, Department of Anesthesiology, University of Tennessee, Memphis, 800 Madison Avenue, Memphis, TN 38163. The University of Tennessee is an Equal Opportunity Employer/Affirmative Action Register/Title IX/Section 504 Employer.

934H/J

ANESTHESIOLOGIST
Multispecialty group of 43 physicians adjacent to 165-bed hospital in need of BC/BE anesthesiologist. Located in West Texas City of 80,000 with excellent recreational activities. Salary guarantee with bonus based on production. Send CV to West Texas Medical Associates, 3555 Knickerbocker Road, San Angelo, TX 76904.

936H/A

NEW ORLEANS
Louisiana State University Medical Center, Department of Anesthesiology, is seeking a board-certified anesthesiologist who is interested in directing publications and research. Outstanding opportunities for clinical studies are available. No night call, weekends, or holidays are required. Excellent salary and fringe benefits. Eligibility for Louisiana licensure is prerequisite. Please send curriculum vitae to M. Naraghi, MD, Professor and Chairman, LSU Department of Anesthesiology, 1532 Tulane Avenue, New Orleans, LA 70140. LSUMC is an EEO/AA employer.

937H/A

OLEAN, N.Y.
Anesthesiologist to join expanding group serving busy hospital in the beautiful Southern Tier. Very competitive salary and benefits. School loans may be forgiven. Send CV to Joseph Kehoe, RR 1, Box 363, Clayton, NY 13624 or call (315) 686-2434 for details.

940H/J

ILLINOIS
Opening for full or part-time BC/BE anesthesiologist to join group practice with academic affiliation. Eleven physicians and 15 CRNAs, cardiothoracic, neuro, neonatal, and OB. Excellent salary and benefits. Send CV to Sangamon Anesthesiologists, St. John's Hospital, 800 East Carpenter, Springfield, IL 62769. (217) 544-3311 (collect).

942H/J

ANESTHESIOLOGIST — BC/BE — Immediate opening. All specialties including cardiac. Excellent salary leading to early partnership. Send CV to Medical Associates, PO Box 141, Minot, ND 58702. (701) 857-5448; FAX (701) 839-8024.

943H/J

PAIN MANAGEMENT TRAINING—ACUTE AND CHRONIC—CA-3 AND FELLOWSHIP POSITIONS
University of Cincinnati Anesthesia Department and the Pain Control Center are seeking applications for Fellowship (preferred) and CA-3 positions in acute and chronic pain management, including cancer pain and pediatric pain management. Chronic benign pain is managed in an interdisciplinary fashion, run by anesthesiologists; program includes inpatient, intensive outpatient, and standard outpatient programs. The Acute Pain Service is aggressive and well accepted, employing all modalities in the management of postoperative and ICU/trauma patients. Opportunities are available for clinical research. Direct inquiries to Donna Benesch, Department of Anesthesia, University of Cincinnati Medical Center, 231 Bethesda Avenue, ML 531, Cincinnati, OH 45267-0531. Phone: (513) 558-6356, FAX: (513) 558-0995.

948H/J

POSTDOCTORAL FELLOWSHIP
Background in clinical medicine or clinical research required for studies with patients with heart disease undergoing surgery. Cardiac function and ischemia assessed with ECG, Holter, and echocardiography monitoring. Working with cardiologists, epidemiologists, and anesthesiologists. Send CV and names of three references to Dennis T. Mangano, PhD, MD, Professor and Vice Chairman, Department of Anesthesia, University of California, San Francisco, 4150 Clement Street (129), San Francisco, CA 94121.

949H/L

FELLOWSHIPS
The Department of Anesthesiology at the University of Alabama at Birmingham offers fellowships for 1–2 years with a 50% to 80% commitment to clinical or bench research with the remaining 20% to 50% commitment to clinical training. Fellowships are available without a research commitment. The fellowships are available in the following areas: (1) *Cardiothoracic Anesthesia*, (2) *Pain Management* (including chronic pain, postoperative pain, pain management of patients with terminal cancer), (3) *Transplantation* (including renal, hepatic, pancreatic, cardiac, and lung), (4) *Neuroanesthesia* (including brain and spinal cord electrophysiological monitoring), (5) *Outpatient Anesthesia*, (6) *Obstetrics*, (7) *Laboratory Research* (pain mechanisms, ischemia-reperfusion injury, nitric oxide, and others). Please send curriculum vitae to Simon Gelman, MD, PhD, Professor and Chairman, Department of Anesthesiology, University of Alabama at Birmingham, 619 South 19th Street, Birmingham AL 35233. An Affirmative Action/Equal Employment Opportunity Employer.

950H/J

CHIEF—CRITICAL CARE DIVISION, ASSOCIATE DIRECTOR—SURGICAL ICU
Department of Anesthesiology, University of Alabama at Birmingham is seeking a board-certified anesthesiologist, certified or eligible in critical care medicine, for Chief—Division of Critical Care and Associate Director—Surgical ICU. Responsibilities include subspecialty resident education in critical care, patient care, research, administration, and recruitment of anesthesiologists-intensivists. Excellent research opportunities. Highly competitive salaries. Contact Simon Gelman, MD, PhD, Professor and Chairman, Department of Anesthesiology, University of Alabama at Birmingham, 619 South 19th Street, Birmingham, AL 35233, (205) 934-4696. An Affirmative Action/Equal Employment Opportunity Employer.

951H/J

BC/BE anesthesiologist for a 500-bed tertiary hospital in a Florida coastal city. Immediate opening. Liberal salary and early partnership. Send resume to Box 956I/L.

956I/L

BOISE, IDAHO—PAIN MANAGEMENT
MD/CRNA group seeking additional BC/BE anesthesiologist with pain fellowship or extensive pain experience for expanding pain clinic. Growing 250-bed hospital soon to be adding a Cancer Institute and Open Heart program. No OB. Great opportunity in progressive community (130,000) located in the foothills. Excellent for family and all types of year-round recreation. Partnership after 1 year. Please respond to William G. Binegar, MD, 6054 Emerald, Boise, ID 83704-8863.

957I/K

COASTAL NEW JERSEY—ANESTHESIOLOGIST DESIRED
Immediate opening for BC or BE MD/DO to join an expanding group practice of 10 MDAs and 9 CRNAs covering a 500-bed regional medical center composed of two hospitals performing over 9000 anesthetics. All types of anesthesia except OH. Great opportunity for energetic well-trained individual. Unlimited opportunity and outstanding lifestyle in a family-oriented seashore community. Very competitive financial package. Please reply with CV to S. Hernberg, DO, Chairman, Department of Anesthesiology, 1925 Pacific Avenue, Atlantic City, NJ 08401.

958I/K

Anesthesiologist to join group consisting of eight anesthesiologists and two CRNAs.

Must be board eligible or board certified. Established PC with many fringe benefits in effect. Send CV to Associated Anesthesiologists of Saginaw, PC, 3121 Davenport, Saginaw, MI 48602 or call (517) 791-2150.

959I/K

PHILADELPHIA, PA.

BC/BE anesthesiologist to join physician/CRNA group in a private, university-affiliated, center-city, tertiary-care hospital. No obstetrics, trauma, or pediatrics. Fellowship experience in open heart anesthesia required. Competitive salary, benefits, and potential for partnership is included. Respond with CV to Box 965I/K.

965I/K

UCSF PEDIATRIC ANESTHESIOLOGY FELLOWSHIP

The Departments of Anesthesia at the University of California, San Francisco and Children's Hospital of Northern California, Oakland, California are jointly offering two 1-year clinical fellowship positions (CA-4) in pediatric anesthesiology beginning *July 1993*. The fellowship will include extensive operating room experience in all pediatric subspecialties in both institutions and critical care medicine exposure for both neonates, older infants, and children. The fellows will spend 6 months in each institution. Send inquiries to Dolores Scholz, Postdoctoral Coordinator, Department of Anesthesia, University of California, San Francisco, Box 0648, San Francisco, CA 94143-0648.

967I/L

ANESTHESIOLOGIST

Department of Anesthesiology at the SUNY Health Science Center in Syracuse, N.Y. is recruiting faculty at the instructor and assistant and associate professor levels. Qualified individuals with a strong academic commitment in all types of anesthesia, critical care, and pain management are sought. SUNY Health Science Center is a tertiary-care center and provides clinical services also to the Syracuse Veterans Administration Hospital. Rank and salary are commensurate with experience. Must be board certified or board eligible and possess a New York State medical license. Please send letter, curriculum vitae, names, addresses, and phone numbers of three references to Enrico M. Camporesi, MD, Professor and Chairman, Department of Anesthesiology, SUNY Health Science Center, Syracuse, NY 13210. The State University of New York Health Science Center is an Equal Opportunity/AA Employer.

968I/K

UNIVERSARY OF CALIFORNIA, DAVIS—

Assistant Professor/Associate Professor/Full Professor

Department of Anesthesiology, University of California, Davis, Medical Center is recruiting for two (2) faculty positions at all ranks. These positions require experience in teaching and clinical training, as well as clinical research. Both positions require demonstrated experience, training, and certification in (1) Critical Care to join two other faculty covering ICU 2–3 months per year; (2) Transplant; and (3) General Anesthesia. These positions are in the nontenured track. Rank and salary are commensurate with experience and based on the UCD School of Medicine Faculty Compensation Plan. Must be board certified or board eligible in anesthesiology, and a California medical license is required. Send curriculum vitae, bibliography, copies of publications, and *the names of three (3) references* to: Dennis Fung, MD, Acting Chairman, Department of Anesthesiology, University of California, Davis, 2315 Stockton Boulevard, Room 2304, Sacramento, CA 95817. Positions are open until filled but not later than December 31, 1992. The University of California, Davis is an Equal Opportunity/Affirmative Action Employer with a strong institutional commitment to the achievement of diversity among its faculty and staff. In that spirit, we are particularly interested in receiving applications from persons of under-represented groups, including women, ethnic minorities, disabled veterans, Vietnam-era veterans, and handicapped persons.

970I/K

ARKANSAS

Pediatric anesthesia fellowship to begin July 1, 1993. Broad-based training in pediatric anesthesia includes experience in cardiac, pain management, and critical care. Active research program. Prefer applicants who have completed CA-3 level in approved residency program. Must be eligible for Arkansas licensure. Send curriculum vitae to Raeford E. Brown, Jr., MD, Chief, Division of Pediatric Anesthesia, Arkansas Children's Hospital, 800 Marshall Street, Little Rock, AR 72202-3591. An Equal Opportunity Employer.

973I/K

DIRECTOR OF OBSTETRIC ANESTHESIOLOGY

The Department of Anesthesiology at the University of Rochester is seeking a Director of Obstetric Anesthesiology, with outstanding qualifications in clinical care, teaching, and research, to assume clinical leadership and to develop advanced education and research programs in obstetric anesthesiology.

Board certification in anesthesiology or its equivalent is required. Academic rank and salary will be commensurate with qualifications. Opportunities for independent or collaborative research are abundant.

Interested candidates should send curriculum vitae to Denham S. Ward, MD, PhD, Professor and Chairman, Department of Anesthesiology, University of Rochester Medical Center, 601 Elmwood Avenue, Rochester, NY 14642. The University of Rochester is an Equal Opportunity Employer.

977IJ

SECOND ANAESTHESIA & CRITICAL CARE SYMPOSIUM—in Ireland

September 11–18, 1993. Sponsored by Yale University School of Medicine (Anesthesia) and Royal College of Surgeons in Ireland. For information and registration contact Postgraduate & Continuing Medical Education, Yale University School of Medicine, 333 Cedar Street, New Haven, CT; (203)-785-4578.

978J

ILLINOIS

Thirty-two physician, well-established, single-specialty group of anesthesiologists seeks additional anesthesiologists. Challenging, broad-based practice encompasses all surgical subspecialties at three hospitals and three ambulatory facilities. Excellent benefits with early partnership. Please send CV to Associated Anesthesiologists, S.C., 5401 North Knoxville, Suite #49, Peoria, IL 61614.

979J/C

MID-SOUTH: ANESTHESIOLOGIST

Immediate opening for BC/BE anesthesiologist at a modern 600-bed teaching hospital and major referral center located in the mid-south. Practice includes cardiac, thoracic, vascular, and general anesthesia as well as intensive care. No obstetrics or pediatrics. Group is to consist of six (6) doctors and 18 CRNAs. Please reply to Clifton W. Emerson, MD, Cardiovascular Anesthesiologists, P.C., 4230 Harding Road, Suite 509, Nashville, TN 37205. Please enclose your current CV.

980J/L

ACADEMIC CRITICAL CARE PEDIATRICIAN

Children's Hospital Medical Center, Cincinnati, Ohio, a 350-bed university-affiliated, teaching hospital, is seeking a full-time director of pediatric critical care. Candidates should be eligible for academic appointment at the associate professor or professor level at the College of Medicine at the University of Cincinnati. Applicants must be board certified or board eligible in pediatric critical care medicine or possess equivalent qualifications. Responsibilities include direction of the clinical program, which has 27 beds and includes a cardiac care unit, a general unit, and isolation facilities; and direction of a pediatric critical care fellowship program. It is anticipated that the successful candidate will have demonstrated productivity in clinical or basic research. Forward applications to Robert W. Wilmott, MD, Chairman, ICU Search Committee, Children's Hospital

Medical Center, Elland and Bethesda Avenues, Cincinnati, OH 45229-2899. Children's Hospital Medical Center is an Equal Opportunity, Affirmative Action Employer.

981J

OBSTETRIC ANESTHESIA FELLOWSHIP
The Department of Anesthesiology at St. Luke's\Roosevelt Hospital Center offers obstetric anesthesiology fellowship positions starting January 1, 1993. The hospital is a University Hospital of Columbia University's College of Physicians and Surgeons, where more than 5000 deliveries are performed annually, many of them high risk. Fellows will participate in the anesthetic management of parturients, resident/medical student teaching, and anesthesiology, perinatology, and neonatology conferences. Research is ongoing and participation is strongly encouraged. Salary and benefits are competitive. For information contact David J. Birnbach, MD, Director of Obstetric Anesthesia, St. Luke's\Roosevelt Hospital Center, Department of Anesthesia, 428 West 59th Street, New York, NY 10019.

982J

UNIQUE FELLOWSHIP OPPORTUNITY COMPLEX AIRWAY MANAGEMENT/HEAD AND NECK ANESTHESIOLOGY
The Department of Anesthesiology and Critical Care Medicine at the University of Pittsburgh Medical Center has created and is now accepting applications for a 6- or 12-month fellowship at the CA-IV level to begin in January of 1993. Based at the Eye and Ear Institute Pavilion at the University of Pittsburgh, clinical mastery in the state-of-the-art management of the complex airway will be emphasized in conjunction with head and neck anesthesiology. Adult and pediatric case variety will encompass head and neck oncology, cranial base surgery, oromaxillofacial surgery, as well as plastic and reconstructive surgery. A multidisciplinary approach involving the Departments of Otolaryngology, Radiology, and Emergency Medicine will be provided. Resources and opportunities exist for ongoing clinical and laboratory investigation. Interested candidates should contact Andrew Herlich, DMD, MD, Assistant Professor of Anesthesiology/Critical Care Medicine and Associate Chief, 230 Lothrop Street, Pittsburgh, PA 15213.

983J

FELLOWSHIP—CARDIAC ANESTHESIOLOGY
CA-3 or CA-4 fellowship position now available in cardiac anesthesia. Busy open heart and vascular service. Opportunity for OR, cath lab, ICU, and clinical research. Excellent salary/benefit package. Send inquiries with CV to Anthony A. Ascioti, MD, Department of Anesthesiology, St. Joseph's Hospital Health Center, 301 Prospect Avenue, Syracuse, NY 13203.

984J/A

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
Faculty position available for board certified/eligible anesthesiologist whose primary clinical responsibilities will be in UCSF's ambulatory surgery facility. Applicants must have at least 5 years of postgraduate training and research experience in the outpatient area. Responsibilities emphasize clinical research, but also include patient care, resident and student teaching, and administrative responsibilities. A California medical license or eligibility for licensure is required. Please forward curriculum vitae to Martin S. Bogetz, MD, Medical Director, UCSF Surgery Center, 400 Parnassus Avenue (A3), San Francisco, CA 94143-0368; (415) 476-8384. The University of California is an Equal Opportunity Affirmative Action Employer.

985JK

PEDIATRIC ANESTHESIA
University of California, San Francisco has faculty positions available for board certified/eligible anesthesiologists with primary interest in pediatric anesthesia. Must have at least 5 years of postgraduate training, including clinical care and research training specific to pediatric patients. Duties include patient care, teaching, research, and administrative responsibilities. California medical license or eligibility for licensure is required. Please forward curriculum vitae and three references to Ronald D. Miller, MD, Professor and Chairman, Department of Anesthesia, UCSF, 521 Parnassus Avenue, Box 0648, Room C-455, San Francisco, CA 94143-0648. The University of California is an Equal Opportunity Affirmative Action Employer.

986JK

LIVER TRANSPLANTATION ANESTHESIA
University of California, San Francisco has faculty positions available for board certified/eligible anesthesiologists with primary interest in liver transplantation. Must have at least 5 years of postgraduate training, including clinical care and research training specific to liver transplant patients. Duties include patient care, teaching, research, and administrative responsibilities. California medical license or eligibility for licensure is required. Please forward curriculum vitae and three references to Ronald D. Miller, MD, Professor and Chairman, Department of Anesthesia, UCSF, 521 Parnassus Avenue, Box 0648, Room C-455, San Francisco, CA 94143-0648. The University of California is an Equal Opportunity Affirmative Action Employer.

987JK

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
Faculty position available in Anesthesia and Critical Care. Applicant must be BC/BE in anesthesia and critical care medicine. Applicant must have at least 5 years of postgraduate training, including research or other intensive care clinical training. Duties include patient care, resident and student teaching, research or specialized clinical activity, and administrative responsibilities. California medical license or eligibility for licensure is required. Send correspondence, curriculum vitae, and list of professional referees to Neal H. Cohen, MD, MPH, MS, Professor and Vice Chairman, Department of Anesthesia, 521 Parnassus Avenue, C450, University of California, San Francisco, CA 94143-0648. The University of California is an Equal Opportunity Employer.

988JK

Excellent CA-4 fellowship opportunity available in Obstetrical Anesthesia at Magee-Womens Hospital, an affiliate of the University of Pittsburgh School of Medicine. Magee-Womens Hospital is the nation's largest private obstetrical tertiary-care hospital performing over 10,000 deliveries annually. Advanced training is provided in the management of normal and high-risk parturients, laboratory and clinical research, and neonatal resuscitation and neonatal intensive care. The fellows are encouraged to supervise junior residents and to prepare didactic scientific presentations. Submit CV and references to Dr. Sivam Ramanathan, Magee-Womens Hospital, Department of Anesthesiology, 300 Halket Street, Pittsburgh, PA 15213-3180.

989J

DON'T FAIL THE WRITTEN BOARDS!
Unique study program including memory devices, methods for improved retention, guessing techniques, etc. Practice questions with answers, explanations and references, new Keywords. Get MEDTEXT not imitations. Call 1-800-695-6301 for information 24 hours. Call 1-800-232-TEXT for orders. MC/V accepted.

933H/A

TUTORING FOR WRITTEN AND ORAL BOARD EXAMS
The unique feature of these programs is the maximum class size of four students. Preparation for the written and oral exams are given separately in 3-day blocks in San Francisco and New York. FOR THE WRITTENS, techniques are taught for dealing with the multiple-choice questions. The basic sciences are stressed. FOR THE ORALS, the guided case discussions are stressed. Home study programs are provided. CALL (415) 321-1117.

763I/B

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For anesthesiologists and CRNAs. We can provide you with quality locum tenens services to meet your specific coverage needs. Or work locum tenens with us for a change in both your practice and your lifestyle. ReplaceMed * 1-800/736-8236 * PO Box 640 * Michigan City, IN 46360.

832A/L

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Providing top-quality CRNAs to meet your specific needs. Our CRNAs are screened to assure quality in performance as well as personal stability. License verification, curriculum vitae, references procured by us, AANA recertification, malpractice verification are supplied to you. Call 1-800-426-2349 any time.

755I/L

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898E/L

A YEAR AHEAD IS NOT TOO SOON!
Start NOW with PHONEPREP! Mock orals, presentation techniques, a systematic approach to oral exam preparation—from the originator of telephone tutorials in anesthesiology. (419) 843-4480.

911J

A WEEKEND OF MOCK ORAL EXAMS
Mock orals, not lectures. We are the original course in this format. 20 hours Category I CME credit, two board-certified instructors, 12 students maximum. Tampa, January 22–24; Dallas, February 19–21; Detroit, March 12–14. ANESTHESIA EXAM REVIEW, 7128 Regents Park, Toledo, OH 43617. (419) 843-4480 or (813) 394-8780.

963J/A

The Osler Institute

Surgery Boards Review Course

October 14-20, 1992 – Chicago

Nov. 6-8 – Cleveland Dec. 11-13 – Chapel Hill Feb. 5-7, '93 – Dalla

Now, your course for written and oral boards offers unlimited mock exam

OBJECTIVES

- Increase knowledge of surgical principles and practice
- Prepare candidates to take written and oral board exams
- Provide a comprehensive review for recertification

METHODS

- HOME STUDY questions, assignments and answers
- SEMINAR with slides and syllabus (Part I course only)
- PRACTICE EXAMS for your oral boards

*"The faculty was outstanding. The most pleasant thing was learning a tremendous amount, not only from world-famous authorities, but from people who are relatively unknown as well."**

Part I Courses:

October 14-20 – Chicago

The Part I Course is designed to prepare candidates for written and oral exams. The course will include home study materials, seven days of lectures with projection slides and syllabus, and practice oral exams. The course in Chicago is immediately before written exams.

Part I Topics

Basic Surgery

Anatomy and Physiology
Anesthesiology
Shock, Fluids and Lytes
Bleeding and Transfusion
Nutritional Support
Surgical Oncology
Transplantation
Infection and Sepsis
Pre- and Post-op. Care

General Surgery

Alimentary Tract
Liver and Gallbladder
Abdomen and Hernia
Pancreas and Spleen
Retroperitoneum
Breast and Skin Tumors
Endocrine Surgery
Head and Neck Surgery
Trauma and Burns
Surgical Critical Care

Special Surgery

Thoracic Surgery
Cardiac Surgery
Vascular Surgery
Orthopedic Surgery
Pediatric Surgery
Urologic Surgery
Gynecologic Surgery
Neurosurgery
Ophthalmology
Plastic Surgery

Faculty

Robert Arensman, M.D.
Robert Bahnson, M.D.
Mimis Cohen, M.D.
John Corson, M.D.
Edward Czinn, M.D.
Robert Feder, M.D.
T. Bruce Ferguson, M.D.
John Fildes, M.D.
Charles Goldman, M.D.
Gerald Harris, M.D.
Edwin Kaplan, M.D.
Mary Jeanne Krob, M.D.
Eberhard Mammen, M.D.
Gary Merlotti, M.D.
Raymond Pollack, M.D.
Harry Richter, M.D.
Natan Scher, M.D.
Joseph Vitello, M.D.
David Vogt, M.D.
Robert Wilson, M.D.

Part II Courses:

November 6-8 – Cleveland
Dec. 11-13 – Chapel Hill
February 5-7, 1993 – Dallas

The Part II Course is designed to prepare board candidates for oral exams. The course will consist of mock oral exams, each based on a presenting problem leading to questions on differential diagnosis, treatment options and complications. Faculty will critique each exam and answer questions.

Each participant will have an exam and critique session and unlimited observation of other sessions. Additional 25-minute sessions may be arranged for $70, and private sessions may be arranged for $100.

Part II Topics

Alimentary Tract
Liver and Gallbladder
Abdomen and Hernia
Pancreas and Spleen
Breast and Skin Tumors
Endocrine Surgery
Head and Neck Surgery
Thoracic Surgery
Vascular Surgery
Trauma Management
Surgical Critical Care

*"...remarkably complete and pleasant...."**

COURSES: The Part I course (consisting lectures and evening mock oral exams) is giv a month before and the week before writt and recertification exams. The Part II cour (mock oral exams) is given for three da before and in the same city as each oral exa Each participant is guaranteed a one-on-o public mock oral and can purchase addition public or private exams. Past participants re ommend repeating our courses, for half pric immediately before your exam.

*"...Accommodations were comfortable...."**

LOCATION: The Part I course will be at th Lisle/Naperville Hilton – 20 miles southwe of Chicago's O'Hare airport. Room rates a $85 for a single and $110 for a double. Th Part II course hotels will be selected in con petitive bidding for the best combination good rates and excellent study environment.

*"...and those little extras...."**

DISCOUNT AIR FARES: Please call toll free (800) 356-7537 for group discount rates.

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FEES AND COURSE HOURS:

Surgeon or Resident:	**Surg.**	**Res.**	**Hr**
• Part I course (7 days):	$810	$540	6.
repeating within 2 years:	$405	$405	6
• Part II course (3 days):	$600	$400	2.
repeating within 2 years:	$300	$300	2
• Extra mock oral exam:	$ 80	$ 80	1/
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CONTRAINDICATIONS: ALFENTA (alfentanil hydrochloride) is contraindicated in patients with known hypersensitivity to the drug.
WARNINGS: ALFENTA SHOULD BE ADMINISTERED ONLY BY PERSONS SPECIFICALLY TRAINED IN THE USE OF INTRAVENOUS AND GENERAL ANESTHETIC AGENTS AND IN THE MANAGEMENT OF RESPIRATORY EFFECTS OF POTENT OPIOIDS. AN OPIOID ANTAGONIST, RESUSCITATIVE AND INTUBATION EQUIPMENT AND OXYGEN SHOULD BE READILY AVAILABLE. BECAUSE OF THE POSSIBILITY OF DELAYED RESPIRATORY DEPRESSION, MONITORING OF THE PATIENT MUST CONTINUE WELL AFTER SURGERY. ALFENTA (alfentanil hydrochloride) administered in initial dosages up to 20 μg/kg may cause skeletal muscle rigidity, particularly of the truncal muscles. The incidence and severity of muscle rigidity is usually dose-related. Administration of ALFENTA at anesthetic induction dosages (above 130 μg/kg) will consistently produce muscular rigidity with an immediate onset. The onset of muscular rigidity occurs earlier than with other opioids. ALFENTA may produce muscular rigidity that involves all skeletal muscles, including those of the neck and extremities. The incidence may be reduced by: 1) routine methods of administration of neuromuscular blocking agents for balanced opioid anesthesia; 2) administration of up to ¼ of the full paralyzing dose of a neuromuscular blocking agent just prior to administration of ALFENTA at dosages up to 130 μg/kg; following loss of consciousness, a full paralyzing dose of a neuromuscular blocking agent should be administered; or 3) simultaneous administration of ALFENTA and a full paralyzing dose of a neuromuscular blocking agent when ALFENTA is used in rapidly administered anesthetic dosages (above 130 μg/kg). The neuromuscular blocking agent used should be appropriate for the patient's cardiovascular status. Adequate facilities should be available for postoperative monitoring and ventilation of patients administered ALFENTA. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.
PRECAUTIONS: DELAYED RESPIRATORY DEPRESSION, RESPIRATORY ARREST, BRADYCARDIA, ASYSTOLE, ARRHYTHMIAS AND HYPOTENSION HAVE ALSO BEEN REPORTED. THEREFORE, VITAL SIGNS MUST BE MONITORED CONTINUOUSLY.
General: The initial dose of ALFENTA (alfentanil hydrochloride) should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining supplemental doses. In obese patients (more than 20% above ideal total body weight), the dosage of ALFENTA should be determined on the basis of lean body weight. In one clinical trial, the dose of ALFENTA required to produce anesthesia, as determined by appearance of delta waves in EEG, was 40% lower in geriatric patients than that needed in healthy young patients. In patients with compromised liver function and in geriatric patients, the plasma clearance of ALFENTA may be reduced and postoperative recovery may be prolonged. Induction doses of ALFENTA should be administered slowly (over three minutes). Administration may produce loss of vascular tone and hypotension. Consideration should be given to fluid replacement prior to induction. Diazepam administered immediately prior to or in conjunction with high doses of ALFENTA may produce vasodilation, hypotension and result in delayed recovery. Bradycardia produced by ALFENTA may be treated with atropine. Severe bradycardia and asystole have been successfully treated with atropine and conventional resuscitative methods. The hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required should be considered in the selection of a neuromuscular blocking agent. Following an anesthetic induction dose of ALFENTA, requirements for volatile inhalation anesthetics or ALFENTA infusion are reduced by 30 to 50% for the first hour of maintenance. Administration of ALFENTA infusion should be discontinued at leas 10-15 minutes prior to the end of surgery. Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists such as naloxone. Because the duration of respiratory depression produced by ALFENTA may last longer than the duration of the opioid antagonist action, appropriate surveillance should be maintained. As with all potent opioids, profound analgesia is accompanied by respiratory depression and diminished sensitivity to CO_2 stimulation which may persist into or recur in the postoperative period. Intraoperative hyperventilation may further alter postoperative response to CO_2. Appropriate postoperative monitoring should be employed, particularly after infusions and large doses of ALFENTA, to ensure that adequate spontaneous breathing is established and maintained in the absence of stimulation prior to discharging the patient from the recovery area.
Head Injuries: ALFENTA may obscure the clinical course of patients with head injuries.
Impaired Respiration: ALFENTA should be used with caution in patients with pulmonary disease, decreased respiratory reserve or potentially compromised respiration. In such patients, opioids may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration.
Impaired Hepatic or Renal Function: In patients with liver or kidney dysfunction, ALFENTA should be administered with caution due to the importance of these organs in the metabolism and excretion of ALFENTA.
Drug Interactions: Both the magnitude and duration of central nervous system and cardiovascular effects may be enhanced when ALFENTA is administered in combination with other CNS depressants such as barbiturates, tranquilizers, opioids, or inhalation general anesthetics. Postoperative respiratory depression may be enhanced or prolonged by these agents. In such cases of combined treatment, the dose of one or both agents should be reduced. Limited clinical experience indicates that requirements for volatile inhalation anesthetics are reduced by 30 to 50% for the first sixty (60) minutes following ALFENTA induction. The concomitant use of erythromycin with ALFENTA can significantly inhibit ALFENTA clearance and may increase the risk of prolonged or delayed respiratory depression. Perioperative administration of drugs affecting hepatic blood flow or enzyme function may reduce plasma clearance and prolong recovery.
Carcinogenesis, Mutagenesis and Impairment of Fertility: No long-term animal studies of ALFENTA have been performed to evaluate carcinogenic potential. The micronucleus test in female rats and the dominant lethal test in female and male mice revealed that single intravenous doses of ALFENTA as high as 20 mg/kg (approximately 40 times the upper human dose) produced no structural chromosome mutations or induction of dominant lethal mutations. The Ames *Salmonella typhimurium* metabolic activating test also revealed no mutagenic activity.
Pregnancy Category C: ALFENTA has been shown to have an embryocidal effect in rats and rabbits when given in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects could have been due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug. No evidence of teratogenic effects has been observed after administration of ALFENTA in rats or rabbits. There are no adequate and well-controlled studies in pregnant women. ALFENTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Labor and Delivery: There are insufficient data to support the use of ALFENTA in labor and delivery. Placental transfer of the drug has been reported; therefore, use in labor and delivery is not recommended.
Nursing Mothers: In one study of nine women undergoing post-partum tubal ligation, significant levels of ALFENTA were detected in colostrum four hours after administration of 60 μg/kg of ALFENTA, with no detectable levels present after 28 hours. Caution should be exercised when ALFENTA is administered to a nursing woman.
Pediatric Use: Adequate data to support the use of ALFENTA in children under 12 years of age are not presently available.
ADVERSE REACTIONS: The most common adverse reactions, respiratory depression and skeletal muscle rigidity, are extensions of known pharmacological effects of opioids. See CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS on the management of respiratory depression and skeletal muscle rigidity. Delayed respiratory depression, respiratory arrest, bradycardia, asystole, arrhythmias and hypotension have also been reported. The reported incidences of adverse reactions listed in the following table are derived from controlled and open clinical trials involving 1183 patients, of whom 785 received ALFENTA. The controlled trials involved treatment comparisons with fentanyl, thiopental sodium, enflurane, saline placebo and halothane. Incidences are based on disturbing and nondisturbing adverse reactions reported. The comparative incidence of certain side effects is influenced by the type of use, e.g., chest wall rigidity has a higher reported incidence in clinical trials of alfentanil induction, and by the type of surgery, e.g., nausea and vomiting have a higher incidence in patients undergoing gynecologic surgery.

Percent	ALFENTA (N=785)	Fentanyl (N=243)	Thiopental Sodium (N=66)	Enflurane (N=55)	Halothane (N=18)	Saline Placebo* (N=18)
Gastrointestinal						
Nausea	28	44	14	5	0	22
Vomiting	18	31	11	9	13	17
Cardiovascular						
Bradycardia	14	7	8	0	0	0
Tachycardia	12	12	39	36	31	11
Hypotension	10	8	7	7	0	0
Hypertension	18	13	30	20	6	0
Arrhythmia	2	2	5	4	6	0
Musculoskeletal						
Chest Wall Rigidity	17	12	0	0	0	0
Skeletal Muscle Movements	6	2	6	2	0	0
Respiratory						
Apnea	7	0	0	0	0	0
Postoperative Respiratory Depression	2	2	0	0	0	0
CNS						
Dizziness	3	5	0	0	0	0
Sleepiness/ Postoperative Sedation	2	8	2	0	0	6
Blurred Vision	2	2	0	0	0	0

*From two clinical trials, one involving supplemented balanced barbiturate/nitrous oxide anesthesia and one in healthy volunteers who did not undergo surgery.

In addition, other adverse reactions less frequently reported (1% or less) were: Laryngospasm, bronchospasm, postoperative confusion, headache, shivering, postoperative euphoria, hypercarbia, pain on injection, urticaria, and itching. Some degree of skeletal muscle rigidity should be expected with induction doses of ALFENTA.
DRUG ABUSE AND DEPENDENCE: ALFENTA (alfentanil hydrochloride) is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and therefore has the potential for being abused.
OVERDOSAGE: Overdosage would be manifested by extension of the pharmacological actions of ALFENTA (alfentanil hydrochloride) (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. No experience of overdosage with ALFENTA was reported during clinical trials. The intravenous LD_{50} of ALFENTA is 43.0-50.9 mg/kg in rats, 72.2-73.6 mg/kg in mice, 71.8-81.9 mg/kg in guinea pigs and 59.5-87.5 mg/kg in dogs. Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression. The duration of respiratory depression following overdosage with ALFENTA may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist should not preclude immediate establishment of a patent airway, administration of oxygen, and assisted or controlled ventilation as indicated for hypoventilation or apnea. If respiratory depression is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled ventilation. Intravenous fluids and vasoactive agents may be required to manage hemodynamic instability.
DOSAGE AND ADMINISTRATION: The dosage of ALFENTA (alfentanil hydrochloride) should be individualized in each patient according to body weight, physical status, underlying pathological condition, use of other drugs, and type and duration of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of ALFENTA should be determined on the basis of lean body weight. The dose of ALFENTA should be reduced in elderly or debilitated patients (see PRECAUTIONS). Vital signs should be monitored routinely. Protect from light. Store at room temperature 15°-30° C (59°-86° F).

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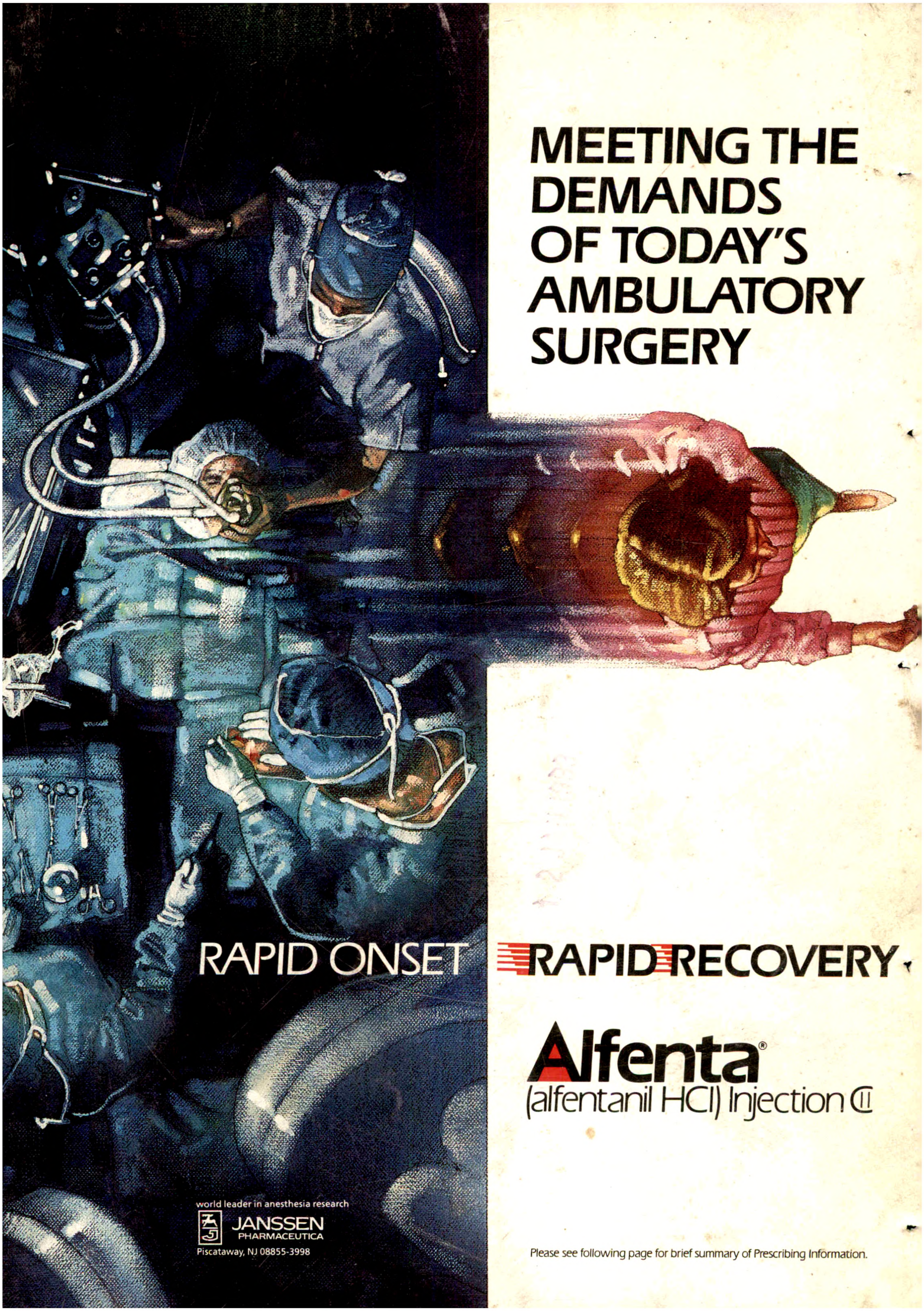

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CLINICAL PHARMACOLOGY OF DESFLURANE

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Desflurane: First New Volatile Anesthetic in Almost 20 Years

John H. Tinker, MD

Department of Anesthesia, University of Iowa, Iowa City, Iowa

The halogenated volatile anesthetics, starting with fluroxene in 1952, with the major advance to halothane in 1956, and then methoxyflurane, enflurane, and isoflurane, have dramatically affected anesthetic practice. Pioneers in this arena including Suckling, Raventos, Johnstone (halothane); Larsen, Artusio, Van Poznak (methoxyflurane); Terrell and Eger (enflurane and isoflurane); Van Dyke and Brown (metabolism and toxicity); Robbins and Eger again (potency); Halsey and Miller (mechanisms) formed an important part of our heritage. Isoflurane, the most recently introduced halogenated volatile anesthetic, was really "ready-to-go" in 1974, but was sidetracked until 1981 by an ill-founded contention that it produced tumors in mice (*lots* of things produce tumors in mice). Most lay people, even most physicians for that matter, have little if any idea just how widely used these drugs are. We do about 27 million anesthetics yearly in the United States alone, of which about 23 million are general anesthetics. Halogenated volatile anesthetics are used in at least *two-thirds* of these. Worldwide, halothane use is still widespread; enflurane is also widely used in Europe, Japan, and Australia; more recently, isoflurane has been introduced in many countries.

As more and more surgery is performed on outpatients, the obvious need exists for anesthesia from which patients can recover rapidly, retain analgesia, be able to perform various self-care activities at home, and hopefully not suffer troublesome nausea and vomiting. Volatile agents have always been critical parts of our training and experience. Even though the "toxic therapeutic ratios" of the agents we use are quite low, implying danger, we are comforted by the relative ease with which we can usually "get it back" if we give too much, and the elegantly simple process of giving such agents by inhalation (now that we have accurate and reliable vaporizers).

On television, the "bad guy" places a handkerchief soaked in some mysterious fluid over a "victim's" face and the victim collapses in a heap in seconds. All of us, faced with various difficult clinical situations, have wished for a safe agent that would induce anesthesia just this fast. In the movies, the hero, badly shot up and operated on all night, comes to perfect alertness just as the heroine enters his (non-intensive care) room. Right.

From the real world, now, comes desflurane. Based on its blood-gas solubility of 0.41, a single-breath induction (perhaps not with a handkerchief) is at least theoretically possible. Changes in anesthetic depth or level are sufficiently fast that experienced anesthesiologists who have used desflurane say things like "its like driving a sports car—you get a constant feel for the patient," and "you feel like you're in better control as stimulus levels change." Our common current practice of discontinuing the volatile agent well before the end of surgery tends to deprive the patient of the agent's muscle relaxant properties. We then must rely on nitrous oxide (which is not a relaxant!) to finish the closure. This practice now conceivably could be modified. Desflurane's relaxant properties could be used almost to the last suture (staple?). The nitrous oxide could be discontinued first. Or perhaps we won't really need nitrous oxide at all with this agent? These possibilities are discussed in this Colloquium.

Problems? Sure there are. Desflurane is sufficiently pungent that our dream of having a "lightning-fast" volatile agent for mask inductions in children will not be realized with this agent. Mask inductions with desflurane in adults and children have been associated with severe coughing and laryngospasm as detailed several places in this Colloquium. Our dream of having a volatile agent that is not a cardiovascular depressant is also not realized with desflurane, despite the fact that there may actually be transient cardiovascular stimulation at relatively fast rates of change in concentration. As its low oil-gas solubility (19:1) predicts, desflurane's potency is only about one-fifth that of isoflurane (MAC between 6% and 7%); a fact that in itself is not necessarily a

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drawback; i.e., there will still be plenty of "oxygen space." Nonetheless, the anesthesiologist will need to develop new mental habits and "time constants." Incremental changes in inspired concentration will often need to be more than 1% at a time, but the time necessary for such an inspired concentration change to produce a clinical effect is much shorter than with the other volatile agents. If your "time constant," i.e., the time you expect to elapse before hemodynamic changes occur, is "set" for isoflurane, you can be unpleasantly surprised at how fast desflurane acts.

Desflurane boils at 23.5°C, i.e., literally in your hand. The required vaporizer is heated and pressurized, with elegant (expensive) electronic controls and safeguards. It probably is *more* accurate than any vaporizer yet produced, owing to the maintenance of a constant temperature and the metering of the agent as a gas, but the fact that it is a new type of vaporizer may be daunting to some.

This Supplement to *Anesthesia & Analgesia* contains reviews that were first presented at a recent colloquium on desflurane held in Florida and sponsored by Anaquest. The presentations were designed to attempt to summarize current knowledge about desflurane in the areas of pharmacokinetics (Dr. Eger); metabolism and toxicity (Dr. Koblin); cardiovascular effects (Dr. Warltier); induction and emergence in adults and pediatric patients (Dr. Smiley); central nervous system effects (Dr. Young); and use in outpatient anesthesia (Dr. White). The presenters at the Colloquium authored the reviews published in this Supplement, but it is to be emphasized that the data summarized in these review articles were gathered from the work of many others. Because the Colloquium was chaired by Dr. Ronald D. Miller of San Francisco, who is also Editor-in-Chief of *Anesthesia & Analgesia*, Dr. Miller asked me, as Associate Editor-in-Chief, to assume editorial control of this Supplement. I was not present at the Colloquium at which these presentations were given and have not directly participated in any of the clinical trials of desflurane.

This Supplement of *Anesthesia & Analgesia* is sponsored by an educational grant from *Anaquest Inc, a Subsidiary of BOC Health Care Inc.* The grant was made to the International Anesthesia Research Society (IARS). *Anesthesia & Analgesia* is the official journal of that Society. No financial benefit from this grant will accrue to any of the authors of the articles contained in this Supplement, or to me as its Editor.

The introduction of desflurane into clinical practice in the United States is anticipated soon, though FDA approval has not been granted as of this writing (May 1992). After careful consideration, the Editorial Board of *Anesthesia & Analgesia*, with the approval of the Board of Trustees of the IARS, agreed that if reviews pertaining to animal and especially human trials of desflurane could be obtained in timely fashion, and if these reviews could be editorially accepted for publication, then *Anesthesia & Analgesia* would publish them collected as a Supplement to the journal.

Some may opine that this is too "close" a relationship with a pharmaceutical manufacturer. It is accepted that the best, indeed the only valid defense against any allegation of conflict of interest is *full and complete disclosure*. I believe the above statements constitute such disclosure. Further, I have gone to considerable effort to assure that the articles contained in this Supplement contain balanced interpretations of the available data. The educational grant made by Anaquest Inc to support publication of this Supplement was made with the full agreement of all parties that there would be no interference with the editorial process. I think the reader will find the presentations balanced and supported by available data. Also included after each article is an edited transcription of the discussion that was held after each presentation at the original Colloquium. I have edited this discussion only in that spoken language has been rendered suitable for publication—I have tried very hard not to alter content of the remarks.

After all that . . . back to desflurane. Will every practicing anesthesiologist want to try the first new volatile halogenated anesthetic to be introduced in almost 20 years? Certainly we will. Whether we will "like" it, and for what kinds of procedures, only time will tell. One thing is certain, anyone who wants to learn to use it will want to be armed with as much data from prior experience as possible. Hopefully, this Supplement will provide a knowledge base to allow us to determine this new agent's place in our pharmacologic toolbox.

Desflurane Animal and Human Pharmacology: Aspects of Kinetics, Safety, and MAC

Edmond I. Eger II, MD

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Substitution of fluorine for the single chlorine atom in isoflurane produces the new anesthetic, desflurane. This seemingly small change produces several pharmacologic changes. The potency of desflurane (MAC equals 6.0% in middle-aged patients) is one-fifth that of isoflurane (1.15%), with MAC for each agent decreased by aging, hypothermia, or the addition of depressants such as midazolam, fentanyl, or nitrous oxide. Some properties are similar: desflurane and isoflurane both depress respiration and neuromuscular contractility, and higher concentrations (e.g., 6%–8% desflurane) of both agents have a pungency that can provoke breath holding, laryngospasm, and salivation, particularly in infants and children. Of great importance, the substitution of fluorine for chlorine markedly decreases blood (desflurane blood-gas partition coefficient 0.42) and tissue solubility (e.g., brain-blood partition coefficient 1.3) relative to isoflurane (values 1.4 and 1.6, respectively). As a result, desflurane alveolar concentrations may be adjusted more rapidly and precisely; desflurane enters and leaves the lungs and tissues more rapidly; and recovery is quicker both for the short (first 10–20 min) and long (0.5–1.5 h) term. This greater precision of control and more rapid recovery are consistent with trends for new drug development in anesthesiology.

(Anesth Analg 1992;75:S3–9)

The drugs that we use in anesthesia are changing. New drugs, such as atracurium, vecuronium, and propofol, have a shorter duration of action and thereby allow greater control over their effects. Desflurane fits this mold. The properties of desflurane, especially those of control and resistance to degradation, promise significant differences from presently available inhaled anesthetics. A discussion of these aspects of pharmacology occupies several of the reports that follow the present account. Some discussions of the pharmacology of desflurane are omitted. For example, there is little or no discussion of its effect on respiration or neuromuscular transmission. These omissions are deliberate: the effects of desflurane on these systems do not differ materially from those of isoflurane and enflurane; these properties are likely to be known to the reader. The respiratory-depressant properties of desflurane are similar to those of isoflurane and enflurane (1–5). Similarly, although desflurane decreases contractility and impairs neuromuscular conduction, thus enhancing the relaxation produced by muscle relaxants, there are no appreciable differences from the effects of isoflurane or enflurane (6–9).

The MAC of desflurane differs from that of other potent agents. Substitution of fluorine for chlorine in isoflurane produces desflurane and, concurrently, decreases potency (10). In rats, the MAC of desflurane is 5.7% (11) to 7.1% (12), in dogs 7.2% (13), in rabbits 8.9% (13), in pigs 10% (14), and in adult humans 6%–7% (1).

The MAC of desflurane decreases with increasing age (Figure 1) (1,15,16). As with other potent inhaled anesthetics (17–19), infants have the highest MAC (15,16). The MAC progressively decreases after a few months of life, in the 45-yr-old patient reaching a value approximately 60% of that of the infant (1). At all age levels, 60% nitrous oxide decreases the MAC of desflurane by approximately 3% desflurane (1,16,20).

As expected, drugs used to supplement anesthesia decrease the MAC. Fentanyl decreases the MAC (20,21) in a dose-dependent fashion at lower serum concentrations but apparently reaches a ceiling at higher levels (21). Fentanyl produces comparable decreases in isoflurane MAC (20). Similarly, midazolam decreases the MAC of desflurane. A premedicant dose of 0.05 mg/kg of midazolam decreases the MAC by 22% without changing the time to recovery (22).

In rats, an increased duration of anesthesia with

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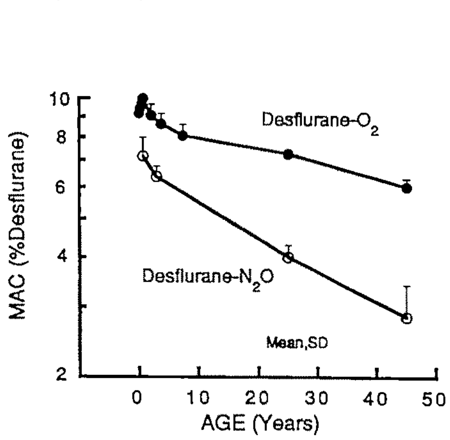

Figure 1. Aging influences desflurane MAC in humans. The MAC reached its zenith at <1 yr of age, decreasing by 40% over the next 45 yr. A parallel effect was seen with nitrous oxide added (1,15,16).

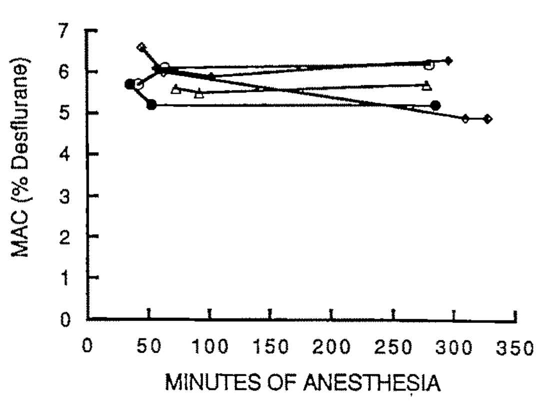

Figure 2. In rats, desflurane MAC measured immediately after anesthesia induction did not differ from that measured after 5 h. Hypothermia was imposed during the interval between these measurements, but the values shown were all obtained in normothermic rats (11).

desflurane does not appreciably change the MAC (Figure 2) (11). As with other anesthetics, MAC decreases with decreased body temperature. In rats, a 10°C decrease in temperature from 38°C decreases the MAC by 42% (Figure 3) (11).

The MAC-awake (the concentration of desflurane that permits an appropriate response to command in 50% of subjects) is 2.42% ± 0.49% (mean ± sd) desflurane (23). The ratio MAC-awake/MAC equals 0.33 ± 0.07 and suggests that desflurane may be a potent hypnotic.

The conversion of isoflurane to desflurane by substitution of a fluorine for a chlorine atom changes much more than anesthetic potency. Indeed, it was predicted that the substitution would produce a much less soluble compound with markedly different kinetics. Results from various investigations indicate that this is so.

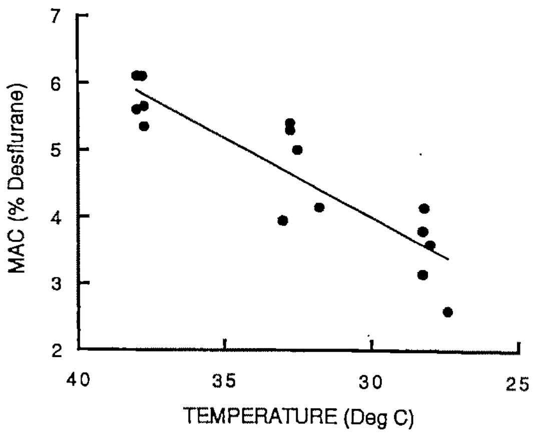

Figure 3. In contrast to the lack of an effect of duration of anesthesia, hypothermia decreased MAC in rats by 0.24% ± 0.04% (mean ± sd) desflurane per °C. Desflurane MAC at 28°C is 58% of the MAC at 38°C (11).

The low desflurane blood-gas partition coefficient, namely 0.42 (24), suggests that its kinetics should approximate those of nitrous oxide (blood-gas partition coefficient 0.47) rather than those of potent but more soluble inhaled anesthetics, such as isoflurane, enflurane, and halothane (Table 1). The increase and decrease of the alveolar concentration of desflurane during induction of and recovery from anesthesia should be more rapid. Similarly, lower tissue-blood partition coefficients for desflurane predict more rapid tissue elimination (Table 1) (25).

Studies in humans and animals confirm these predictions (23,26–28). The alveolar concentration of desflurane (FA) increases toward the concentration inspired (FI) more rapidly (i.e., the FA/FI ratio approaches 1.0 more rapidly) than with other potent anesthetics (Figure 4) (23,26,27). However, despite the near identity of their partition coefficients, the increase in FA/FI is more rapid with nitrous oxide than with desflurane because of augmentation provided nitrous oxide by the concentration effect (29). The results depicted in Figure 4 came from studies in which nitrous oxide was administered at an inspired concentration of 65% and desflurane at only 2%.

Similarly, during elimination, the rate of decrease of the desflurane alveolar concentration (relative to the last alveolar concentration during anesthetic administration (FAO)) exceeds that of all other potent inhaled anesthetics (Figure 5) (26,27). Because of lower tissue-blood partition coefficients for desflurane, the difference between desflurane and other anesthetics widens with increasing duration of elimination (Figure 6). After 5 days, the FA/FAO ratio for desflurane is one-tenth that of sevoflurane, which in turn has an FA/FAO ratio approximately one-third that of isoflurane or halothane. Results from studies in swine confirm these results in humans (28).

Percutaneous loss of other inhaled anesthetics exceeds that of desflurane, but such loss does not influence pharmacokinetics in humans for any agent (30,31). For all anesthetics, visceral losses from an

Table 1. Human Blood-Gas and Tissue-Blood Partition Coefficients of Inhaled Anesthetics[a]

Blood or tissue	Desflurane	Sevoflurane	Isoflurane	Halothane
Blood	0.42 ± 0.02	0.68 ± 0.05	1.46 ± 0.09	2.54 ± 0.18
Brain	1.3 ± 0.1	1.7 ± 0.1	1.6 ± 0.1	1.9 ± 0.2
Heart	1.3 ± 0.2	1.8 ± 0.2	1.6 ± 0.2	1.8 ± 0.3
Liver	1.3 ± 0.1	1.8 ± 0.2	1.8 ± 0.2	2.1 ± 0.3
Kidney	1.0 ± 0.1	1.2 ± 0.2	1.2 ± 0.2	1.0 ± 0.2
Muscle	2.0 ± 0.6	3.1 ± 1.0	2.9 ± 1.0	3.4 ± 1.4
Fat	27 ± 3	48 ± 6	45 ± 6	51 ± 10

For the blood-gas partition coefficients, $n = 11$ (desflurane), 19 (sevoflurane), 16 (isoflurane), and 15 (halothane). For the tissues studied, $n = 10$ (liver, kidney), 8 (muscle, heart, fat), and 6 (brain).
Values are shown as mean ± SD.
[a]Data are from Yasuda et al. (25), Strum and Eger (40), and Eger and Eger (42).

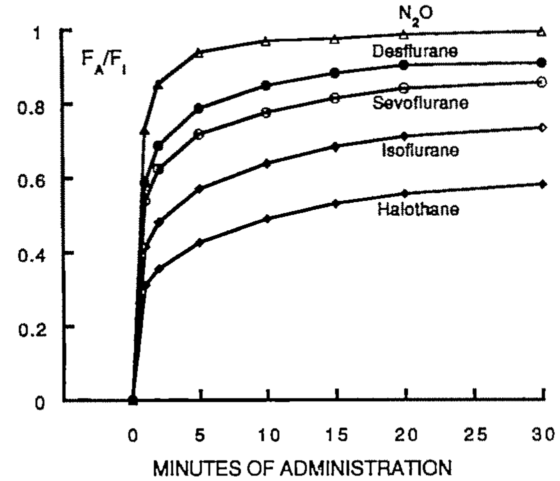

Figure 4. In humans, alveolar concentration (FA) of desflurane increased toward inspired concentration (FI) more rapidly than that of other potent inhaled anesthetics. Except for nitrous oxide, the position of each graph is consistent with the blood-gas partition coefficient of each agent. Nitrous oxide had a more rapid increase than desflurane because its increase (but not that of desflurane) was influenced by the concentration effect (29).

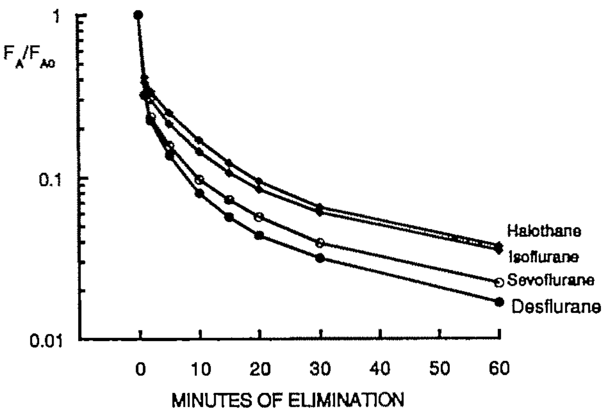

Figure 5. As defined by the decreased alveolar concentration relative to the last alveolar concentration found during anesthesia (FAO), desflurane is eliminated in humans more rapidly than are other potent agents.

opened abdomen or thorax are larger than cutaneous losses (32). Again, the rate of loss for desflurane is less than that for other potent agents. Similarly, despite the greater rate of loss, the total movement from viscera to air does not materially influence the kinetics of any of the anesthetics.

The more rapid increase and decrease of desflurane in alveoli is reflected in the brain. In rabbits, the increase in cerebral anesthetic partial pressure (CC) relative to FI is most rapid with desflurane, less with isoflurane, and slowest with halothane (33). Similarly, cerebral anesthetic elimination (CC/FAO) proceeds more rapidly with desflurane than with isoflurane or halothane (Figure 7).

These data suggest that induction of and recovery from anesthesia with desflurane may be more rapid than with other potent inhaled anesthetics. This prediction is correct for recovery but not for induction. Although volunteers given "square-wave" concentrations of up to 5.4% desflurane breathed ". . . without coughing, breath-holding, salivation or other untoward respiratory response" (34), such concentrations are less than those required for induction of anesthesia. Concentrations of 6%–8% can evoke coughing, breath holding, laryngospasm, and salivation (1,35). The airways of children are irritated as much as the airways of adults by the pungency of desflurane (36,37). Irritation is at least as great (and may be greater) with desflurane as with isoflurane (35). Consistent with these studies of airway irritability, the pungency of desflurane slows induction of anesthesia by inhalation (37).

Although pungency limits rate of induction with desflurane, it does not limit rate of recovery. Studies of recovery in animals are of particular interest, because studies in humans may be confounded by factors such as use of adjuvant drugs or imposition of surgery. Studies in animals also permit precise control of anesthetic dose and duration.

Rate of recovery from anesthesia was studied in rats (38) by noting time from termination of anesthetic administration to successful completion of a

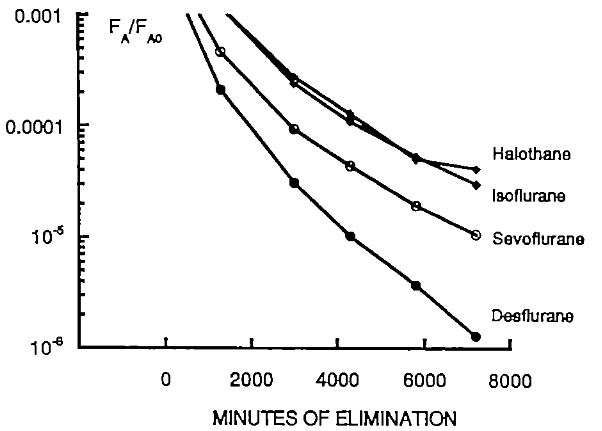

Figure 6. As recovery progresses, differences between desflurane and other agents portrayed in Figure 5 increased due to smaller tissue-blood partition coefficients of desflurane. After 5 days, FA/FAO of desflurane is less than one-tenth that for the other agents. (Abbreviations as in Figures 4 and 5.)

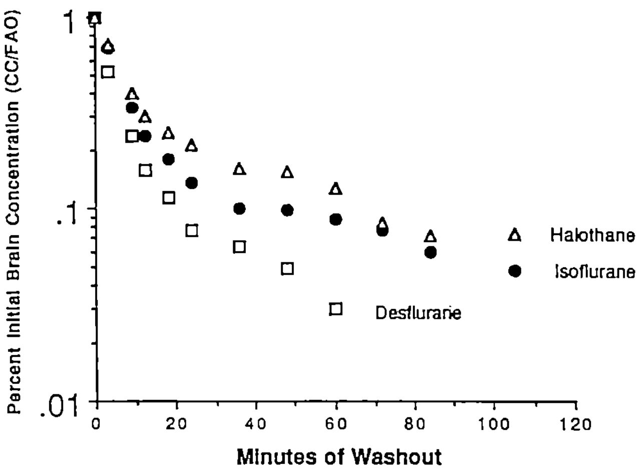

Figure 7. In live rabbits, nuclear magnetic resonance measurements of anesthetics demonstrate cerebral elimination of desflurane that is severalfold more rapid than that of isoflurane or halothane (33).

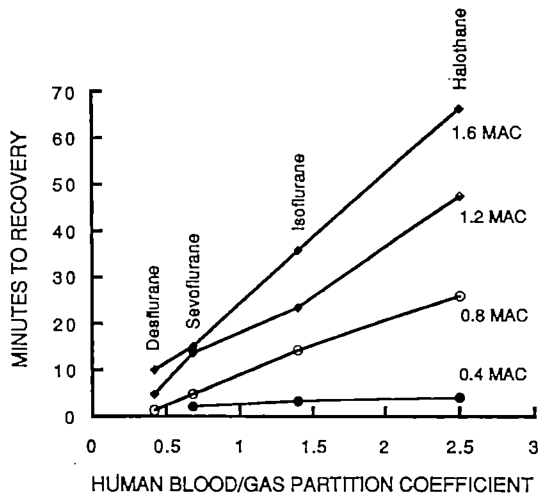

Figure 8. For a given concentration of anesthetic and duration of administration in rats, recovery from anesthesia occurred at a rate that is a rectilinear function of solubility (38). The slopes defining this relationship increased with increased anesthetic concentration. The points at a blood-gas partition coefficient of 0.42 are for desflurane, at 0.69 for sevoflurane, at 1.4 for isoflurane, and at 2.5 for halothane.

task demanding muscle coordination (the Rotarod test [39]). Anesthetics tested were desflurane, sevoflurane (blood-gas partition coefficient 0.69) (40), isoflurane (1.4) (41,42), and halothane (2.4) (42). For a given MAC multiple and duration of anesthesia, rate of recovery was inversely related to blood solubility and, therefore, was always most rapid with desflurane (Figure 8). Although increased duration of anesthesia or increased concentration lengthened recovery time for all anesthetics, the increase was least with desflurane.

Rate of recovery after a given dose and duration correlates with the blood-gas partition coefficient (Figure 8). These data indicate that blood-gas partition coefficients of 0.3–0.4 provide near-maximal rates of recovery. Extrapolation of each graph yields a zero intercept (of the abscissa) at partition coefficients of 0.3–0.4. At these partition coefficients, recovery rate cannot be accelerated further by decreasing solubility. Recovery at such low blood-gas partition coefficients is likely to be affected by cerebral rather than pulmonary clearance. The results of these studies of elimination and recovery in animals have implications to patient management that will be discussed by others in this Colloquium.

Anesthetics can dissolve in circuit components. Such solution can retard anesthetic administration and elimination (43,44). Because desflurane is less soluble in plastic and rubber components found in anesthetic circuits (45), such solution will have less effect on desflurane kinetics than on kinetics of other potent agents. Desflurane washes into and out of an anesthetic circuit (without connection to a patient) more rapidly than isoflurane (45). Although the difference between the two agents is significant, uptake and elimination of anesthetic for either agent are too small to materially affect anesthesia.

In summary, the molecular structure of desflurane distinguishes this new agent from presently available potent inhaled anesthetics. Desflurane is less potent, having a MAC that is five times greater than the MAC of isoflurane. It is much less soluble in tissues and blood, having a blood-gas partition coefficient that is one-third that of isoflurane. The pungency of desflurane prevents it from providing a faster induction of anesthesia, but its solubility properties permit closer control of anesthetic depth and more rapid recovery from anesthesia than is possible with presently available agents.

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DISCUSSION

DR. JOHN KAMPINE (Milwaukee): You commented that it is your observation that MAC-awake correlates with creation of amnesia. Is there a difference among those three agents that you indicated on the slide insofar as their ability to produce amnesia relating to MAC-awake?

DR. EDMOND I. EGER II (San Francisco): Not too much in relation to MAC-awake for desflurane and isoflurane. It would appear that nitrous oxide is less of an amnestic agent than is isoflurane, there being a factor of 2 difference between the two.

DR. KAMPINE: You showed the slide that indicated the constancy of desflurane anesthesia over time, but I did not hear you comment about how this compares with other agents.

DR. EGER: Other agents (isoflurane, halothane, and cyclopropane) are similarly constant.

DR. KAMPINE: Some studies indicate differences in physiologic responses at constant levels of anesthesia for prolonged periods of time, and there are differences of opinion about what causes that. I do not think it has ever been resolved. Is desflurane the same or different with regard to that property of the halogenated agents?

DR. EGER: There are some differences, late versus early, but they are relatively small. Some would suggest increased beta activity, but we did not test that. There are differences in peripheral resistance, and there are some differences in heart rate, I believe, but the majority of cardiovascular effects are not particularly different with regard to early versus late.

DR. SUJIT PANDIT (Ann Arbor): You showed two slides on washout curves; looking at halothane and isoflurane, despite the fact that their solubilities are so different, their washout was almost identical. Yet, in recovery, isoflurane was much faster. Is there anything that I am missing apart from the solubility, something that makes it a quicker recovery?

DR. EGER: The difference between isoflurane and halothane, we believe, is related to a difference in their metabolic degradation, with isoflurane not being degraded and halothane being degraded. The concentrations that were applied during the studies in human volunteers, the ones where you remarked on the identity of the washout curves, were concentrations at relatively low levels. We know that the metabolism of halothane is a saturable phenomenon in which higher concentrations produce a limit to the rate at which metabolism occurs, the Vmax being associated with a concentration of perhaps 1/20th to 1/50th of MAC itself. Thus, if you apply higher concentrations of halothane and of isoflurane, you will be more apt to reveal the difference between the two agents, and we did apply higher concentrations in rats. That is speculation, but I believe that it accounts for the difference you noted.

DR. JERROLD LERMAN (New York): With respect to desflurane kinetics, you suggested that its lower solubility would allow a more rapid adjustment of anesthesia depth. There is no question that elimination will be a reflection of the drug's solubility. However, the washin of this anesthetic, or rather the induction of anesthesia in allowing us to reach greater depths of anesthesia, should be no different than it is with other agents because of overpressure. If we do not use overpressure, then desflurane would allow us greater control, but in clinical terms, this drug will not allow us to achieve greater anesthesia depth more rapidly than any other more soluble inhaled agent.

DR. EGER: You bring up a good point, and I stand corrected. It is true that we can raise anesthesia level equally as rapidly with isoflurane or halothane or, for that matter, even with methoxyflurane, as we can with desflurane, if we are prepared to supply sufficient overpressure. The difference, though, is that the stability of the alveolar value you obtain using a higher pressure will be less with a more soluble agent. If you apply overpressure, you will have a constantly rising concentration with a more soluble agent, unless you carefully titrate to the level that you want. If you apply a level of desflurane, you go to that level and stay there, because of its lower solubility. That brings up another point. Do we need to have a desflurane analyzer for this new agent? My answer is that it would be nice to have one, but if we are talking about need (i.e., relative need), we have less need for an analyzer for this agent than with any other potent inhaled agent because what you give (i.e., inspired) is what you get (expired). The difference between delivered concentration and what is in the patient's alveoli, blood, and brain is going to be less with this agent than with other agents. If you have an accurate vaporizer, you have a good idea of alveolar concentration; as well as that in the brain.

DR. JOSEPH R. ARTUSIO, JR. (New York): Why does changing one chlorine for one fluorine atom change the biologic potency so significantly in this compound?

DR. EGER: If you change from chlorine to fluorine in any organic compound, you decrease lipid solubility, which, as the Meyer-Overton rule would predict, should decrease potency. The change in potency is essentially identical to what you would predict in terms of lipid solubility. The next question is, why does the conversion to fluorine change lipid solubility? I am not enough of a physical chemist to answer that question.

DR. DONALD WALLACE (Dallas): Has single-breath induction been tested with desflurane?

DR. EGER: Yes, single-breath induction has been tested. Anesthesia can be induced very rapidly with desflurane.

DR. ARTUSIO: We looked at single-breath induction. We observed considerable breath holding when the subject takes a single breath at a concentration of 1 or 2 MAC. If you induce anesthesia slowly, you can achieve similar anesthesia with much less upper airway irritation.

DR. EGER: I would add that in studies by Dr. Ronald Jones, 6% desflurane was administered as a square wave. He observed no coughing, no breath holding, and no secretions.

DR. ROBERT G. MERIN (Houston): Has the respiratory response to surgical incision been studied with desflurane? Does the incision partially antagonize the anesthetic?

DR. IRA RAMPIL (San Francisco): We did not examine it rigorously. My impression during surgical anesthesia was that respiration increased if it had been slow. This did not appear to be different from isoflurane. Dr. Yasuda studied the circulatory response to stimulation, which seemed to be abolished at deeper levels of anesthesia (i.e., 1.6 or 1.7 MAC levels). If the respiratory responses are similar, it may be that desflurane does differ from isoflurane in that aspect.

DR. RONALD D. MILLER (San Francisco): You concluded that desflurane was outstanding and that a skillful clinician could save costs by eliminating use of muscle relaxants. What data did you present to support that conclusion?

DR. EGER: I said that neuromuscular effects of desflurane and isoflurane were essentially identical. I then reasoned that if you could deepen anesthesia without concern for delaying recovery, you could take advantage of the property of desflurane or isoflurane that allows essentially complete paralysis at deeper levels. Desflurane and isoflurane or halothane provide relaxation sufficient to permit endotracheal intervention. Deeper levels of anesthesia, Dr. Caldwell has shown, diminish neuromuscular transmission. We believe you could perform almost any procedure without muscle relaxants if you are willing to give a deep enough level of anesthesia with this compound.

DR. R. D. MILLER: You have stated that you can do the same thing with isoflurane, is that correct?

DR. EGER: Yes.

DR. R. D. MILLER: I cannot speak about desflurane because I have not administered desflurane, but with isoflurane, it is not the delayed recovery that prevents me from administering higher concentrations. It is predominantly the cardiovascular effects. Is that true with desflurane?

DR. EGER: Yes. I think it would also be true. If cardiovascular effects are your concern, then you may not be able to administer deeper levels. On the other hand, with desflurane we can now dispense with nitrous oxide and obtain the (muscle relaxant) benefit of desflurane at lighter levels of anesthesia, which we are not inclined to do with isoflurane because of the potential for delaying recovery.

Characteristics and Implications of Desflurane Metabolism and Toxicity

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The metabolism of desflurane has been assessed both in animals and humans by measuring the appearance of fluoride metabolites (fluoride ion, nonvolatile organic fluoride, trifluoroacetic acid) in blood and urine. Desflurane administered to rats (either pretreated or not pretreated with phenobarbital or ethanol) for 3.2 MAC-hours and to swine for 5.5 MAC-hours produced fluoride ion levels in blood that were almost indistinguishable from values measured in control animals. In contrast, a significant 17% increase in plasma fluoride ion concentration in swine was detected 4 h after exposure to desflurane. In human studies, desflurane administered to patients (3.1 MAC-hours) and volunteers (7.35 MAC-hours) resulted in postanesthesia serum fluoride in concentrations that did not differ from background fluoride ion concentrations. Similarly, postanesthetic urinary excretion of fluoride ion and organic fluoride in volunteers was comparable to preanesthetic excretion rates. Small but statistically significant levels of trifluoroacetic acid were found in both serum and urine from volunteers after exposure to desflurane. Peak serum concentrations averaging 0.38 ± 0.17 μM trifluoroacetic acid (mean ± SD) and peak urinary excretion rates averaging 0.169 ± 0.107 μmol/h were detected in volunteers 24 h after desflurane exposure. Although these increases in trifluoroacetic acid after exposure to desflurane were statistically significant, they are approximately 10-fold less than levels seen after exposure to isoflurane. Desflurane strongly resists biodegradation, and only a small amount is metabolized in animals and humans.

(Anesth Analg 1992;75:S10–6)

Desflurane (formerly I-653) has several desirable characteristics, including the capacity to produce rapid induction and emergence and flexibility in adjusting depth of anesthesia (1–5). Another desirable attribute of a volatile anesthetic is that the compound should resist biotransformation and be devoid of organ-specific toxicity (1). One might predict that desflurane would be a relatively stable molecule, as it differs from isoflurane (relatively resistant to degradation) only by substitution of a fluorine atom for a chlorine atom. Fluorine substitution for other halogens generally tends to increase biologic stability. Such stability is reflected in vitro by increased resistance by desflurane to degradation by soda lime compared with other volatile anesthetics (6).

Metabolism of desflurane is of interest because of potential connections between metabolism and toxicity. Toxicity might result from generation of fluoride ion after metabolic breakdown (e.g., impaired renal function) (7) or from breakdown products that covalently bind to proteins and lipids (e.g., hepatic toxicity) (8). The metabolism of desflurane has been examined both in animals and humans. The animal studies allow control of variables (e.g., diet, medications) that are difficult or impossible to control in the perioperative clinical setting and also allow modeling of various conditions (e.g., induction of liver enzymes) that might promote biotransformation. Studies in humans are also required, because marked species differences may exist in drug metabolism (9). Safety of an anesthetic in animals does not ensure safety in humans.

Animal Studies

In rats, serum fluoride ion concentration was measured after administration of desflurane (I-653) for 2 h at an inspired concentration of 1.6 MAC (10) (Figure 1). Rats were either not pretreated or were pretreated with phenobarbital (1 mg/mL in drinking water for 5 days) or ethanol (16% [vol/vol] in drinking solution for 14 days) to induce production of liver enzymes. Rats pretreated with phenobarbital exhibited a small but statistically significant increase in serum fluoride

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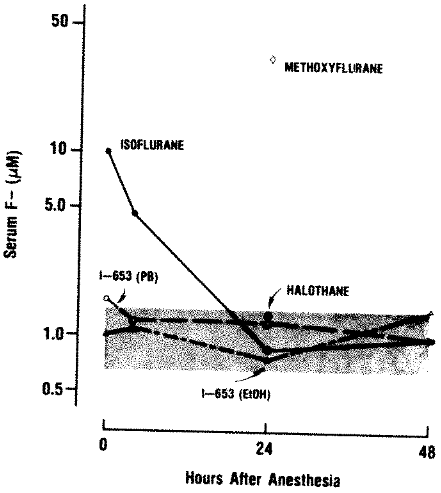

Figure 1. Serum concentrations of fluoride ion in rats pretreated with phenobarbital (PB) or ethanol (EtOH) and anesthetized with 1.6 MAC desflurane (I-653) for 2 h. The shaded rectangular area represents the mean value (1.0 μM) ± SD (0.37 μM) of serum fluoride ion in control rats pretreated with phenobarbital but not exposed to anesthetic. For animals given desflurane, only the value measured immediately after exposure (1.6 ± 0.5 μM; $n = 8$) in the phenobarbital-pretreated rats significantly differed from control. Serum fluoride concentrations achieved after exposure of phenobarbital-pretreated rats to isoflurane, halothane, and methoxyflurane are from data in Koblin et al. (10).

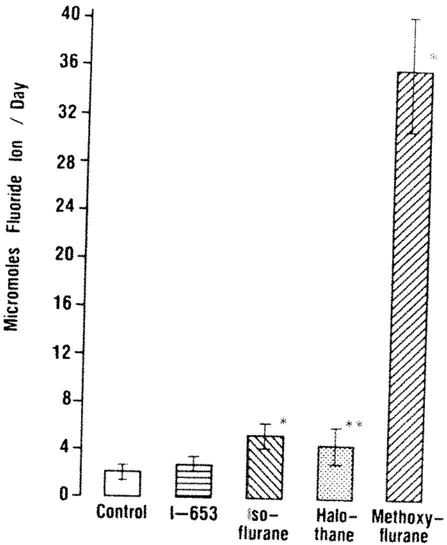

Figure 2. Twenty-four-hour excretion of fluoride ion in urine of rats pretreated with phenobarbital and anesthetized with 1.6 MAC desflurane (I-653), isoflurane, halothane, or methoxyflurane for 2 h. Control rats were pretreated with phenobarbital but not exposed to anesthetic. Error bars represent ± SD. *$P < 0.001$; **$P < 0.05$. (Figure constructed from data in Koblin et al. [10].)

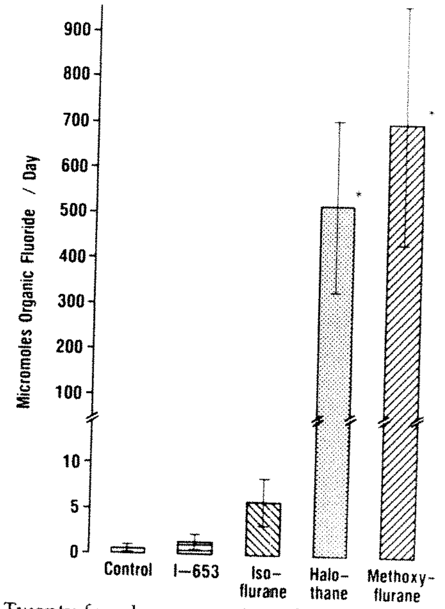

Figure 3. Twenty-four-hour excretion of nonvolatile organic fluoride in urine of rats pretreated with phenobarbital and anesthetized with 1.6 MAC desflurane (I-653), isoflurane, halothane, or methoxyflurane for 2 h. Control rats were pretreated with phenobarbital but not exposed to anesthetic. Error bars represent ± SD. Note discontinuity in ordinate for halothane and methoxyflurane. *$P < 0.001$. (Figure constructed from data in Koblin et al. [10].)

ion concentration immediately after, but not 4, 24, or 48 h after, desflurane exposure (10) (Figure 1). No increased fluoride ion could be detected in the serum of either nonpretreated or ethanol-pretreated rats after desflurane exposure (Figure 1). Rats pretreated with phenobarbital and given 1.6 MAC isoflurane for 2 h had peak serum levels of fluoride ion seven- to tenfold higher than unanesthetized control rats or rats given desflurane for an equivalent number of MAC-hours. Marked increases in serum fluoride ion also occurred after exposure to methoxyflurane (Figure 1). Urinary excretion of fluoride ion was not significantly increased in rats pretreated with phenobarbital and exposed to desflurane, whereas urinary fluoride ion excretion did increase after exposure to the other volatile agents (Figure 2). Similarly, urinary excretion of nonvolatile organic fluoride in rats pretreated with phenobarbital was not elevated in rats given desflurane (Figure 3). Rats pretreated with ethanol and exposed to desflurane demonstrated 24-h excretion of urinary organic fluoride nearly ten times greater than in controls (10).

In swine, fluoride ion concentrations were measured in plasma samples taken before, immediately after, and 4 h after exposure to either desflurane or isoflurane (11). Each anesthetic was administered at concentrations between 0.7 and 1.6 MAC to a total dose of approximately 5.5 MAC-hours for each agent. Plasma fluoride ion concentrations immediately after and 4 h after exposure to isoflurane were approximately 300% greater than values obtained in awake swine before anesthesia (Figure 4). In contrast, swine given desflurane had no detectable elevations in plasma fluoride concentration immediately after an-

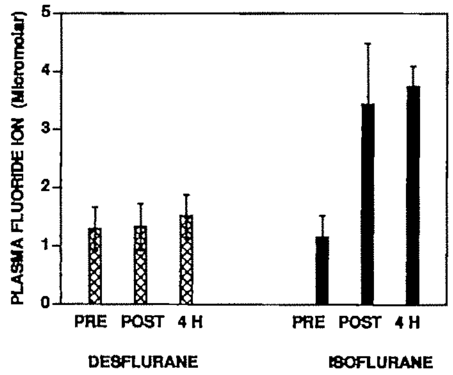

Figure 4. Plasma concentrations of fluoride ion in swine before (PRE), immediately after (POST), and 4 h after anesthesia with desflurane or isoflurane for 5.5 MAC-hours. For desflurane, the value for 4 h after anesthesia (1.51 ± 0.36 μM; n = 8) was significantly higher than that obtained in awake swine before anesthesia (1.29 ± 0.37 μM). Error bars represent ± SD. (Figure constructed from data in Koblin et al. [11].)

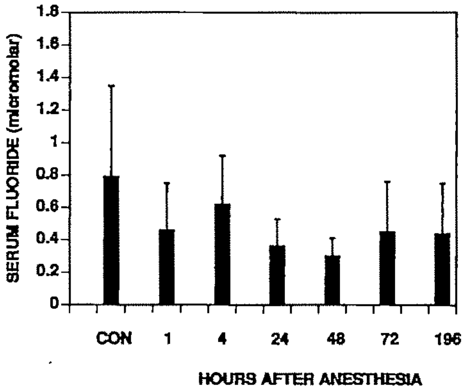

Figure 5. Serum concentrations of fluoride ion in 10 young male human volunteers before anesthesia (CON) and at various times after anesthesia with desflurane (average concentration of 3.6% administered for approximately 90 min). No value after anesthesia differed significantly from before anesthesia. Means are given. Error bars represent + SD. (Figure constructed from data in Jones et al. [17].)

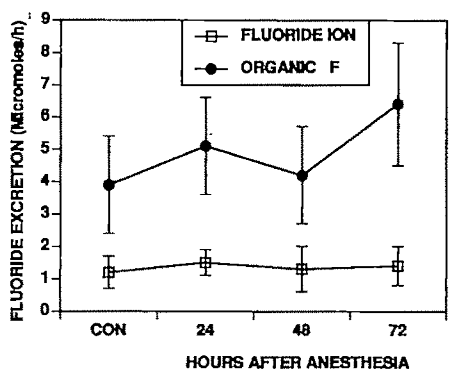

Figure 6. Excretion of fluoride ion and nonvolatile organic fluoride in urine of volunteers before anesthesia (CON) and at 24, 48, and 72 h after anesthesia with desflurane (average concentration 3.6% administered for approximately 90 min). No value after anesthesia differed significantly from before anesthesia. Means are given. Error bars represent ± SD. (Figure constructed from data in Jones et al. [17].)

esthesia but had a (significant) 17% increase in plasma fluoride ion concentration 4 h after anesthesia (Figure 4).

In vitro, the biotransformation of desflurane in a guinea pig liver slice culture system was minimal, with sixfold less fluoride ion produced from desflurane than from isoflurane (12). These results are consistent with the findings in rats and indicate that desflurane is metabolized less than isoflurane.

The resistance of desflurane to metabolic breakdown is associated with a lack of tissue toxicity. In rats pretreated with phenobarbital and exposed for 1 h to 12% O_2 and no anesthesia (control) or to 1.2 MAC desflurane, isoflurane, or halothane, no hepatic injury occurred in control rats or those given desflurane (13). In contrast, 100% of the halothane-exposed and 20% of the isoflurane-exposed rats had hepatic injury (13). No tissue damage in brain, pituitary, lung, heart, duodenum, pancreas, kidney, or liver attributable to desflurane could be detected in rats given a total of six 2-h exposures over two consecutive weeks to 1.6 MAC desflurane in oxygen (14). In swine receiving 5.5 MAC-hours of desflurane (or isoflurane) with or without several anesthetic adjuvants, no elevation in plasma alanine aminotransferase activities was detected immediately after anesthesia or 1 day after or 4–7 days after desflurane, again implying that desflurane did not cause hepatic injury (15). In a guinea pig liver slice culture system, 2.2 mM desflurane caused a mild reduction in tissue K^+ content and decreased protein synthesis (12). The effects of desflurane were less than those of isoflurane (12). The concentration (2.2 mM) of desflurane used in these studies was relatively high, corresponding to a partial pressure of approximately 25% of 1 atm, or approximately four times MAC (16).

Human Studies

The first studies to test for possible metabolic breakdown of desflurane in humans were performed by Jones et al. (17). Ten volunteers exposed to an average concentration of 3.6% desflurane for approximately 90 min exhibited no increases in serum fluoride ion (Figure 5) or in urinary fluoride excretion (Figure 6). These initial studies in humans did not provide evidence for the metabolism of desflurane, but they may not have constituted a sufficient test because of the limited duration and concentrations of desflurane that were applied. The studies were repeated in volunteers given prolonged exposure to desflurane, sometimes at high concentrations (18). Trifluoroacetic acid, a sensitive marker of desflurane metabolism that was not assayed in the early studies,

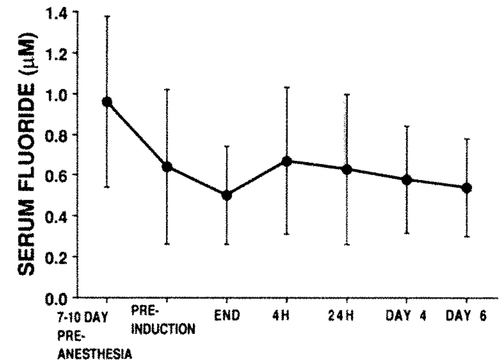

Figure 7. Serum fluoride ion concentrations in volunteers anesthetized with desflurane (7.35 ± 0.81 MAC-hours). Values were obtained 7–10 days before anesthesia ($n = 12$); immediately before anesthesia ($n = 13$); at end of anesthesia ($n = 8$); and at 4 h ($n = 12$), 24 h ($n = 13$), 4 days ($n = 13$), and 6 days ($n = 13$) after anesthesia. Error bars indicate ± SD. There was no statistically significant change between preanesthetic and postanesthetic concentrations of serum fluoride ion. (Reproduced from Sutton et al. [18] with permission from the International Anesthesia Research Society.)

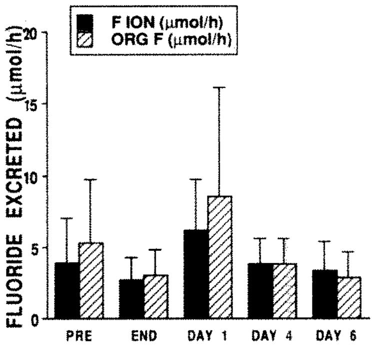

Figure 8. Urinary excretion rates of fluoride ion and organic (ORG) fluoride in volunteers anesthetized with desflurane (7.35 ± 0.81 MAC-hours). Values were obtained 7–10 days before anesthesia ($n = 11$); at end of anesthesia ($n = 5$); and at 24 h ($n = 13$), 4 days ($n = 13$), and 6 days ($n = 12$) after anesthesia. Error bars indicate + SD. There was no statistically significant change between preanesthetic and postanesthetic urinary excretion rates of either fluoride ion or organic fluoride. (Reproduced from Sutton et al. [18] with permission from the International Anesthesia Research Society.)

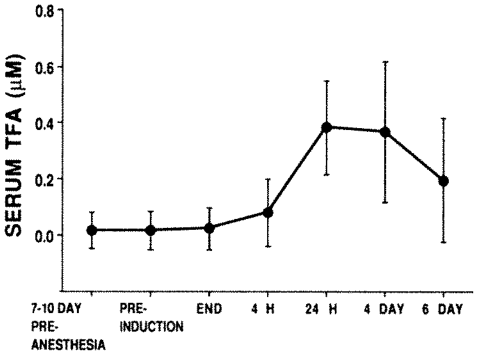

Figure 9. Serum trifluoroacetic acid (TFA) concentrations in volunteers anesthetized with desflurane (7.35 ± 0.81 MAC-hours). Values were obtained 7–10 days before anesthesia ($n = 12$); immediately before anesthesia ($n = 13$); at the end of anesthesia ($n = 9$); and at 4 h ($n = 11$), 24 h ($n = 13$), 4 days ($n = 13$), and 6 days ($n = 13$) after anesthesia. Error bars indicate ± SD. Trifluoroacetic acid levels were significantly elevated, maximal (0.38 ± 0.17 μmol/L) at 24 h after anesthesia, and remained significantly elevated above background at 6 days after desflurane anesthesia. (Reproduced from Sutton et al. [18] with permission from the International Anesthesia Research Society.)

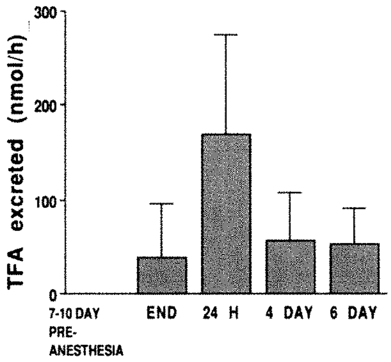

Figure 10. Urinary excretion rates of trifluoroacetic acid (TFA) in volunteers anesthetized with desflurane. Values were obtained at 7–10 days before anesthesia ($n = 12$); at the end of anesthesia ($n = 7$); and at 24 h ($n = 13$), 4 days ($n = 13$), and 6 days ($n = 11$) after anesthesia. Error bars indicate + SD. The excretion rate of trifluoroacetic acid was significantly elevated above background just after anesthesia. The excretion rate was maximal (0.169 ± 0.107 μmol/h) at 24 h after anesthesia and remained significantly increased 6 days after anesthesia. (Reproduced from Sutton et al. [18] with permission from the International Anesthesia Research Society.)

was measured after prolonged exposure to desflurane (18).

Thirteen volunteers anesthetized with desflurane for an average of 6.81 ± 0.55 h (±SD) (total dose of desflurane of 7.35 ± 0.81 MAC-hours) did not increase postanesthesia serum fluoride ion concentrations compared with background levels (18) (Figure 7). Also, urinary excretion of fluoride ion and organic fluoride in these volunteers did not significantly increase after prolonged exposure to desflurane (Figure 8). Trifluoroacetic acid did appear in the serum of volunteers exposed to desflurane (Figure 9). Serum trifluoroacetic acid levels were significantly elevated 24 h after desflurane exposure and remained elevated in 6 of 13 volunteers 6 days after desflurane exposure (Figure 9). Urinary excretion of trifluoroacetic acid increased significantly above a nondetectable background rate in volunteers (Figure 10). This increase was detected in four volunteers immediately after desflurane anesthesia and was found in all volunteers 24 h after anesthesia. Urinary excretion of trifluoroacetic acid was maximal 24 h after desflurane anesthesia and was still evident 6 days after anesthesia (Figure 10).

Patients were given desflurane without increasing fluoride ion levels in serum. In 26 ASA physical status I and II patients given desflurane for an average of 3.08 MAC-hours, concentrations of fluoride ion in serum immediately after the operation and on postoperative days 1 and 3 did not differ from values obtained before anesthesia (18). These results were confirmed in a separate study in which 12 patients were given desflurane for approximately 2 MAC-hours with no detectable increases in plasma fluoride immediately after surgery compared with the preoperative levels (19).

The resistance of desflurane to biodegradation is also apparent in isolated human tissue. Microsomes prepared from livers of organ donors were examined for capacity to defluorinate methoxyflurane, sevoflurane, enflurane, isoflurane, and desflurane (20). Of these volatile agents, the least amount of fluoride production was seen with desflurane (20).

Humans given desflurane exhibited no evidence of tissue toxicity. Liver function tests (serum levels of total and unconjugated bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and γ-glutamyltranspeptidase) were unchanged in volunteers (17) and patients (21). Renal function tests (urinalysis, plasma urea, plasma creatinine, creatinine clearance, and excretion of retinol-binding protein and β-*N*-acetyl-D-glucosaminidase) also remained normal after desflurane given to volunteers (17) and patients (21).

Discussion and Conclusion

The close structural resemblance of desflurane to isoflurane makes it reasonable to expect desflurane metabolism to resemble that of isoflurane. Isoflurane metabolism is thought to involve breakdown by cytochrome P-450 to yield fluoride ion and certain organofluorine products that may be ultimately converted to trifluoroacetic acid (22). Thus, if desflurane is metabolized, increased amounts of fluoride ion and organic fluoride products (specifically trifluoroacetic acid) should appear in blood and urine after exposure.

Increased blood concentrations of fluoride ion after desflurane anesthesia could only be detected in phenobarbital-pretreated rats immediately after anesthetic exposure (Figure 1) and in nonpretreated swine 4 h after desflurane anesthesia (Figure 4). These increases, though significant, were small. No increased serum fluoride levels could be detected in humans given desflurane (Figures 5 and 7). Definitive evidence for metabolism of desflurane in humans is provided by appearance of trifluoroacetic acid in serum (Figure 9) and in urine (Figure 10) after desflurane exposure.

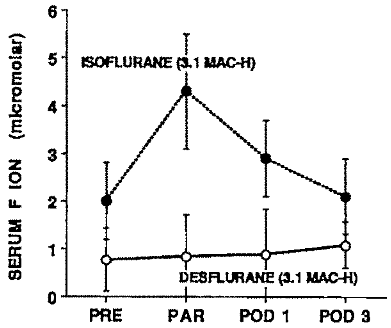

Figure 11. Serum fluoride ion concentrations in patients anesthetized with desflurane from Sutton et al. (18) compared with Mazze et al. (23), where patients were anesthetized with isoflurane. Error bars indicate ± SD. Serum fluoride levels were increased above background after exposure to isoflurane. There was no significant increase in serum fluoride ion concentrations after exposure to desflurane. PRE, before anesthesia; PAR, postanesthesia recovery; POD, postoperative day. (Reproduced from Sutton et al. [18] with permission from the International Anesthesia Research Society.)

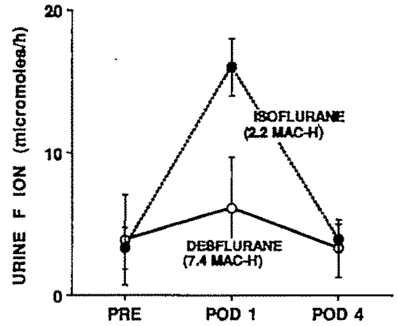

Figure 12. Urinary excretion rates of fluoride ion in volunteers receiving desflurane from Sutton et al. (18) compared with Hitt et al. (24), where patients were anesthetized with lower average doses of isoflurane. Error bars indicate ± SD. Fluoride ion excretion rate increased above background after isoflurane exposure. There was no significant increase in urinary fluoride ion excretion rate after desflurane exposure. (Reproduced from Sutton et al. [18] with permission from the International Anesthesia Research Society.)

Inability to detect elevated levels of fluoride ion in serum and urine after desflurane exposure contrasts with the findings of previous studies of isoflurane (23,24), which demonstrated elevated concentrations of fluoride ion in serum (Figure 11) and urine (Figure 12) of surgical patients. Higher concentrations of fluoride ion in urine were found after anesthesia with isoflurane, even though lower average doses of isoflurane (24) than desflurane were administered (Figure 12). Smiley et al. (19) reported a significant increase in plasma fluoride ion concentration at the end of an operation in patients receiving isoflurane but not in those receiving desflurane, suggesting that desflurane resists biodegradation more than isoflurane.

Mean serum trifluoroacetic acid concentrations (Figure 9) and mean urine trifluoroacetic acid excretion rates (Figure 10) in volunteers at 24 h, 4 days, and 6 days after exposure to desflurane were significantly elevated, with a peak mean serum concentration of 0.38 μM at 24 h. This serum trifluoroacetic acid concentration after desflurane anesthesia is approximately 1000-fold lower than the concentration of approximately 500 μM achieved after the administration of 0.44%–1.57% end-expired halothane for 2 h to patients undergoing intraabdominal surgery (25). Comparison with isoflurane is difficult because only limited data are available for trifluoroacetic acid production after isoflurane administration in humans. In patients who have received isoniazid, peak serum trifluoroacetic acid concentrations are on the order of 10 μM after isoflurane anesthesia (26). The peak mean excretion rate of trifluoroacetic acid in urine after exposure to desflurane (0.169 μmol/h [Figure 10]) is approximately 100-fold less than that observed after exposure of patients to lower average doses of isoflurane (approximately 50 μmol/h [23]).

The findings in selected animal and human studies of slight increases in fluoride ion or trifluoroacetic acid levels above background after exposure to desflurane demonstrate that a small degree of metabolism does occur. This presumes that extent of anesthetic metabolism is proportional to serum fluoride ion, organic fluoride, and trifluoroacetic acid concentrations in serum and urine. Although this assumption is reasonable, it is possible that higher levels of metabolites might have resulted under conditions that promote synthesis of hepatic microsomal enzymes. For example, in rats pretreated with ethanol (10), excretion of nonvolatile organic fluoride in urine for 1 day after desflurane exposure was approximately ten times greater than control. The possibility also remains that desflurane degradation products could be sequestered (e.g., in bone or liver), or covalently bind to tissues and not appear in blood, or that breakdown products are excreted by the lungs rather than in serum or urine. Such processes do not occur to a large extent, because mass balance studies performed in human volunteers demonstrate complete recovery of desflurane (27).

Low levels of fluoride metabolites in serum and urine after desflurane anesthesia suggest, but do not prove, that desflurane is unlikely to be tissue toxic. This has been confirmed in animal (12–15) and human studies (17,21). A theoretical potential for desflurane hepatotoxicity by cross-sensitivity with other inhaled anesthetics cannot be excluded (8). The mechanism of cross-sensitivity might be production of low levels of trifluoroacetic acid after desflurane administration, with subsequent covalent reaction between trifluoroacetic acid and protein to form hapten (antigen) (Figure 13). If a patient previously received a different volatile anesthetic (e.g., halothane, isoflurane) that undergoes metabolism to trifluoroacetic acid, and if that resulted in antibodies directed against trifluoroacetyl antigens, then these antibodies could theoretically react against newly formed trifluoroacetyl antigens after hepatic degradation of desflurane and cause liver damage (8). This possibility is extremely remote and has yet to be demonstrated for isoflurane.

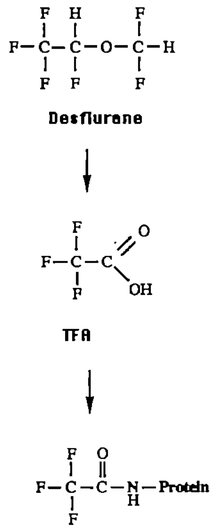

Figure 13. Theoretical production of trifluoroacetyl protein hapten (antigen) after hepatic degradation of desflurane to trifluoroacetic acid (TFA).

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DISCUSSION

DR. RONALD D. MILLER (San Francisco): At what point do problems occur with production of fluoride metabolites; that is, at what point do they not occur? Do we have problems with isoflurane in this regard?

DR. DONALD D. KOBLIN (San Francisco): Isoflurane is thought to produce minimal effects from its metabolism, but such effects are possible. For instance, in a recently published article (Murray et al., Anesth Analg 1992;74:236–40), plasma fluoride concentrations during and after prolonged exposure to isoflurane (19 MAC-hours) reached as high as 70 μmol in the serum, a concentration that is associated with nephrotoxicity. Although there was no clinical evidence of renal dysfunction in that report, you become concerned at those fluoride ion concentrations.

DR. JERROLD LERMAN (New York): I take exception to the suggestion that a single plasma or serum level of fluoride ion is associated with nephrotoxicity. I think from a pharmacologic point of view, we are concerned about the area under the concentration-time profile (i.e., how long the kidney is exposed to various concentrations of fluoride ion), not isolated peak values.

DR. ROBERT G. MERIN (Houston): Sensitivities to fluoride ion levels vary. What you really need is an antidiuretic hormone (ADH) challenge test as a sensitive method to detect renal dysfunction. I do not believe there has been a clinically proved case of nephrogenic diabetes insipidus with enflurane. My question is, what about the possible formation of a hapten when trifluoroacetic acid reacts with proteins? Is that something we have to be concerned about? Are we back to halothane-type concerns?

DR. EDMOND I. EGER II (San Francisco): With regard to Dr. Lerman's comment, the area under the curve and peak height of serum fluoride concentrations are both inadequate measures. Obviously, if kidney damage were only related to the area under the curve, we would all be in trouble, because we are chronically exposed to levels of anywhere from 1 to 5 μM fluoride ion. So it cannot simply be area under the curve. As has been pointed out, it cannot simply be due to the peak concentration achieved. In answer to the comment that enflurane nephrotoxicity has never really been shown; I agree that it has not. With desflurane, I do not think it is nephrotoxicity that should concern us; rather, it is hepatotoxicity. Direct hepatotoxicity from desflurane is unlikely, because there simply is not a sufficient amount broken down. On the other hand, because trifluoroacetic acid results from desflurane metabolism, a risk could be that of hapten formation. As Dr. Merin implied, the amount of hapten that is likely to be formed from desflurane metabolism surely is less than that from isoflurane, and he questions whether there has ever been a valid case of isoflurane-induced hepatotoxicity. Although there has not yet been a definitive study, I think we can say that to date we have not found a proved case of isoflurane hepatotoxicity. If it is that rare with isoflurane, we are likely to have trouble finding a case with desflurane if the hepatotoxicity is related to the combination of trifluoroacetic acid with protein.

DR. CHARLES COTÉ (Boston): There are circumstances where prolonged anesthesia will take place. In our hospital we perform finger reimplants that can last anywhere from 12 to 48 h. Almost always, these patients are anesthetized with a potent agent because of the projected duration of surgery and because we do not want to administer large amounts of narcotic. As another example, there are reports of using potent agents to treat refractory status epilepticus as well as refractory status asthmaticus.

DR. KOBLIN: There have been studies in which isoflurane was administered for up to 2 days to control convulsive status epilepticus refractory to standard therapy (Kofke et al. Anesthesiology 1989;71:653–9). Serum fluoride concentrations measured in those studies were on the order of 10 μM and were without clinically apparent adverse effects.

Cardiovascular and Respiratory Actions of Desflurane: Is Desflurane Different From Isoflurane?

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The cardiovascular and respiratory effects of desflurane are reviewed. In experimental animals, desflurane has been shown to produce hemodynamic effects comparable to those produced by isoflurane. Desflurane increases heart rate and decreases both mean arterial pressure and systemic vascular resistance while maintaining cardiac output. In some but not all studies, desflurane has appeared to maintain arterial pressure and systemic vascular resistance to a somewhat greater degree than equianesthetic concentrations of isoflurane. Otherwise, desflurane and isoflurane produce strikingly similar effects on systemic, coronary, renal, hepatic, and cerebral circulation. In addition, desflurane and isoflurane have nearly identical actions on a variety of indices of left ventricular systolic and diastolic function. Although desflurane may cause coronary vasodilation in dogs, no evidence of "coronary steal" has been observed in a canine model of multivessel coronary artery disease. In humans, desflurane produces alterations in systemic hemodynamics that have many similarities to those produced in animals. No differences between the cardiovascular actions of desflurane and isoflurane have been identified in volunteers during spontaneous or controlled ventilation with and without nitrous oxide. Desflurane and isoflurane also produce similar hemodynamic effects during induction and maintenance of anesthesia in a wide variety of clinical settings. To date, no direct evidence of desflurane-related myocardial ischemia or increased cardiovascular morbidity has been observed in patients with coronary artery disease. Desflurane depresses ventilation in animals and humans. Dose-related decreases in tidal volume and increases in respiratory rate, arterial carbon dioxide tension, dead space/tidal ventilation ratio, and intrapulmonary shunt fraction have all been observed in volunteers. These effects are similar to those produced by other currently used volatile anesthetics, including isoflurane. Desflurane, like isoflurane, also appears to be a mild respiratory irritant. Thus, the cardiorespiratory effects of the new volatile anesthetic, desflurane, are remarkably similar to those produced by isoflurane.

(Anesth Analg 1992;75:S17–31)

Desflurane (difluoromethyl-1-fluoro-2,2,2-trifluoroethyl ether [I-653]) is the first new volatile anesthetic to undergo clinical trials in the United States in almost 20 yr. A structural analogue of isoflurane, desflurane possesses remarkable metabolic stability (1–4) and has very low blood- and tissue-gas partition coefficients (5,6), which may facilitate rapid anesthetic induction, alterations in anesthetic depth, and emergence. The hemodynamic actions of desflurane and its effects on respiratory function have been explored in experimental animals and in humans over the past 4 yr. The purpose of this review is to summarize those investigations describing the cardiovascular and respiratory actions of desflurane and to compare and contrast these effects with those produced by isoflurane.

Cardiovascular Actions of Desflurane in Experimental Animals

Using chronically instrumented swine mechanically ventilated to maintain normocarbia, Weiskopf et al. (7) examined the cardiovascular effects of desflurane at end-tidal concentrations of 0.8, 1.2, and 1.6 MAC and directly compared these effects to those produced by near-equianesthetic concentrations of isoflurane. Desflurane caused an increase in heart rate that was greatest at 0.8 MAC, with dose-related decreases in mean arterial pressure. Cardiac output was maintained at the low concentration of desflurane but decreased in dose-related fashion at 1.2 and 1.6 MAC. Decreased systemic vascular resistance

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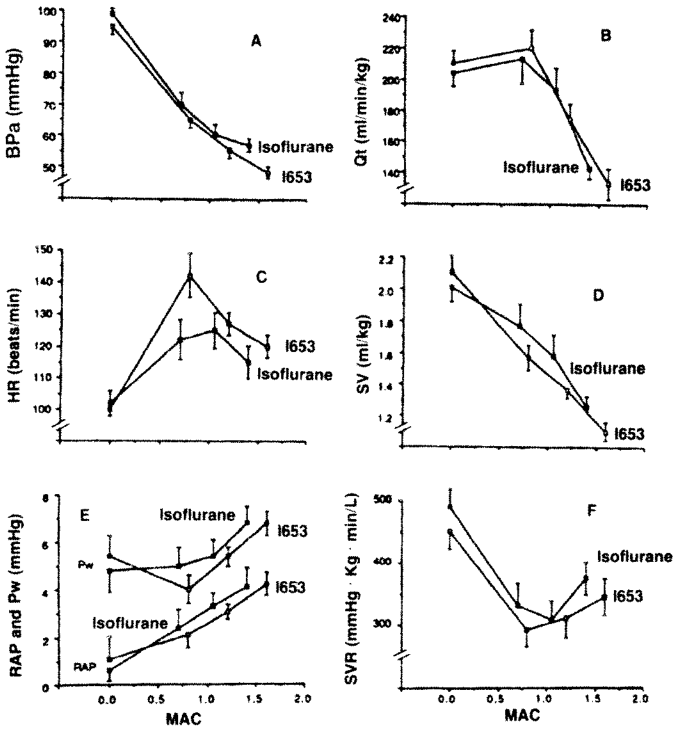

Figure 1. Hemodynamic effects of desflurane (I-653) (*open squares*) and isoflurane (*solid squares*) in chronically instrumented swine: **(A)** mean aortic blood pressure (BPa); **(B)** cardiac output (Qt); **(C)** heart rate (HR); **(D)** stroke volume (SV); **(E)** right atrial pressure (RAP) and pulmonary capillary wedge pressure (Pw); **(F)** systemic vascular resistance (SVR). (Modified from original figure of Weiskopf et al. [7]. With permission of authors and publisher.)

(SVR) was observed at the lowest concentration but was not further depressed at higher concentrations. Right atrial pressure and pulmonary capillary wedge pressure increased dose dependently (Figure 1). This implied depression of systemic hemodynamics and myocardial function; however, desflurane did not affect overall tissue perfusion, because oxygen transport and consumption and mixed venous oxyhemoglobin saturation were essentially unchanged from the conscious state at all levels of anesthetic depth. In addition, no alterations in base excess or blood lactate levels were observed during desflurane anesthesia, consistent with maintenance of adequate cellular perfusion. The cardiovascular effects of desflurane were not distinguishable from those produced by near-equianesthetic isoflurane concentrations.

Weiskopf et al. (8) subsequently explored the cardiovascular safety of high concentrations of desflurane and isoflurane in swine. Using the ratio of lethal to anesthetic concentration as an index of margin of safety, the authors determined that the ratio of fatal anesthetic concentration to MAC for desflurane was less (2.5) than the ratio for isoflurane (3.0) but greater than the ratio reported for halothane (2.0) (9). They speculated that the concentration of desflurane producing cardiovascular collapse was greater than that resulting in apnea, and thus cardiovascular compromise during spontaneous ventilation was considered unlikely. The dose-response relationships produced by desflurane and isoflurane for heart rate, mean aortic blood pressure, and cardiac output were similar except in concentrations >1.5 MAC, where these variables were better maintained with isoflurane than with desflurane. This study suggested that desflurane may produce more profound cardiovascular depression than isoflurane when administered in concentrations >1.5 MAC. As in the previous investigation (7), however, mixed venous oxyhemoglobin saturation and the ratio of oxygen transport to oxygen consumption remained constant in both groups up to 2 MAC and decreased only when the anesthetic concentration was increased to near-fatal concentrations, indicating that compromise of tissue perfusion occurred only at very high concentrations of either agent.

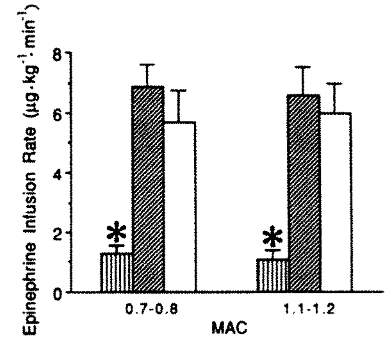

Figure 2. Intravenous infusion rates of epinephrine required to produce greater than three premature ventricular contractions per minute in swine anesthetized with desflurane (*hatched bar*), isoflurane (*open bar*), and halothane (*vertically striped bar*) at 0.7–0.8 and 1.1–1.2 MAC. Anesthetic concentration used did not alter rate of epinephrine infusion required to produce ventricular ectopy. *Significantly ($P < 0.05$) different from epinephrine infusion rate producing premature ventricular contractions in desflurane group. (Original figure from Weiskopf et al. [10]. Reproduced with permission of authors and publisher.)

Weiskopf et al. (10) investigated the arrhythmogenic potential of desflurane in response to administration of epinephrine in swine. The rate of infusion of epinephrine needed to cause premature ventricular contractions during anesthesia with desflurane was similar to that required during equianesthetic isoflurane anesthesia. Epinephrine infusions resulted in similar increases in mean arterial pressures and heart rate in both desflurane and isoflurane groups. Ventricular ectopy occurred at lower infusion rates of epinephrine when swine were anesthetized with halothane (Figure 2).

Weiskopf et al. (11) also studied the cardiovascular effects of drugs commonly administered during anesthesia in the presence of desflurane or isoflurane in swine. Atracurium, succinylcholine, and atropine plus edrophonium had no cardiovascular effects in swine anesthetized with 1.2 MAC desflurane or isoflurane. Fentanyl (50 and 100 μg/kg IV) caused no cardiovascular effects during either anesthetic, except for a modest increase in SVR at the high dose. Sixty percent nitrous oxide caused no cardiovascular changes during desflurane anesthesia but did increase SVR and decrease cardiac output and stroke volume during isoflurane anesthesia. Thiopental (2.5 and 5.0 mg/kg IV) decreased mean aortic blood pressure, cardiac output, stroke volume, and SVR during both anesthetics without altering heart rate or filling pressures. Naloxone (100 μg/kg IV) decreased SVR and increased cardiac output during both desflurane and isoflurane anesthesia but increased heart rate only during isoflurane anesthesia. In summary, anesthetic adjuvants used in usual clinical doses during desflurane anesthesia did not produce unexpected or potentially disadvantageous cardiovascular effects. Desflurane and isoflurane again produced similar hemodynamic alterations in both anesthetic groups.

The cerebral and systemic hemodynamic effects of desflurane in acutely instrumented dogs were reported in three investigations by Milde and coworkers (12–14). Desflurane was found to produce significant decreases in cerebrovascular resistance and increased cerebral blood flow consistent with cerebral vasodilation (12). Desflurane also caused dose-related decreases in mean arterial pressure and SVR with relative maintenance of cardiac index, supporting the findings of Weiskopf et al. (7) in swine. Similar hemodynamic actions were also observed in the response of canine cerebral circulation to hyperventilation during desflurane anesthesia (13). Desflurane also provided adequate cerebral perfusion to meet the demands of cerebral oxygen consumption during profound desflurane-induced hypotension (mean arterial pressure 40 mm Hg) (14). These parallel decreases in cerebral blood flow, and oxygen consumption, and maintenance of adequate cerebral perfusion were similar to those previously described for halothane and isoflurane (15,16); however, the systemic hemodynamic effects produced by desflurane differed from those previously reported (7,8,10–12). The decrease in mean arterial pressure observed by Milde and Milde (14) resulted primarily from decreased cardiac output and not reduced SVR. This relative maintenance of SVR occurred despite high end-tidal concentrations of desflurane (15.5% ± 0.3% [mean ± SEM]; 2.2 MAC) and suggested that desflurane-induced hypotension resembled that produced by halothane (15) and not isoflurane (16). This conclusion is not entirely consistent, however, because adequate tissue perfusion was maintained during desflurane-induced hypotension similar to findings observed during isoflurane-induced hypotension (16). These results are in contrast to those observed when halothane was used to decrease blood pressure, because anaerobic metabolism was observed at high halothane concentrations (15). No changes in heart rate occurred with desflurane administration in the investigation by Milde and Milde (14), in contrast to previous studies (7,8,10–12) that indicated that desflurane may inhibit baroreceptor reflex functions similar to halothane but not isoflurane. High baseline heart rates were observed in this acute experimental preparation that used neuromuscular blockade with pancuronium. Although the systemic hemodynamic effects of desflurane were not directly compared with those produced by isoflurane in this study (14), the results suggested that important differences may exist between these agents.

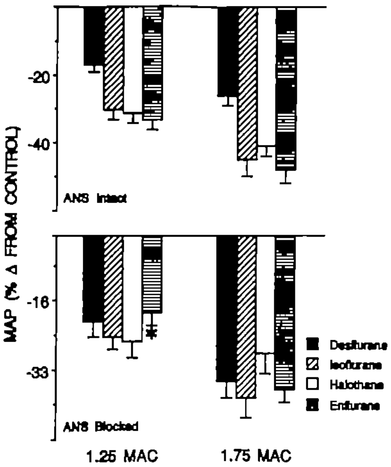

Figure 3. Histograms depicting effects of volatile anesthetics (1.25 and 1.75 MAC) on mean arterial pressure (MAP) in autonomically (ANS) intact versus blocked chronically instrumented dogs. All values significantly ($P < 0.05$) different from baseline conscious control. Desflurane reduced MAP less ($P < 0.05$) than isoflurane, enflurane, or halothane in ANS intact dogs (*upper panel*). Effect was abolished with ANS blockade (*lower panel*). *Significantly ($P < 0.05$) different from same anesthetic at same concentration in ANS intact dogs. (Original figure from Pagel et al. [17]. Reproduced with permission of authors and publisher.)

The systemic and coronary hemodynamic actions of desflurane were studied in the presence and absence of intact autonomic nervous system function and directly compared with the effects produced by isoflurane, halothane, and enflurane in chronically instrumented dogs in an investigation by Pagel et al. (17). Although many similarities between the hemodynamic effects of desflurane and isoflurane were identified, some differences between these anesthetics were noted as well. Desflurane maintained mean arterial pressure to a greater degree than did equianesthetic concentrations of isoflurane (up to 1.75 MAC) (Figure 3). Whereas isoflurane produced decreased SVR, no changes in resistance were ob-

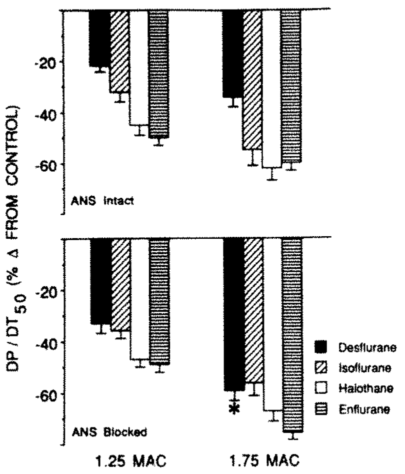

Figure 4. Histograms depicting effects of volatile anesthetics (1.25 and 1.75 MAC) on left ventricular dP/dt$_{50}$ (an index of myocardial contractility) in autonomically (ANS) intact versus blocked chronically instrumented dogs. All values are ($P < 0.05$) different from baseline conscious control. Desflurane reduced dP/dt$_{50}$ significantly less ($P < 0.05$) than isoflurane, halothane, or enflurane in ANS intact dogs (*upper panel*). Effect was abolished by ANS blockade (*lower panel*). *Significantly ($P < 0.05$) different from same anesthetic at same concentration in ANS intact dogs. (Original figure from Pagel et al. [17]. Reproduced with permission of authors and publisher.)

served with desflurane, supporting the findings of Milde and Milde (14). Desflurane appeared to maintain myocardial contractility, as assessed by left ventricular peak positive dP/dt and dP/dt$_{50}$ to a greater extent than did equianesthetic concentrations of isoflurane in dogs with intact autonomic nervous system function (Figure 4). These differences between isoflurane and desflurane were abolished with pharmacologic autonomic nervous system blockade (Figures 3 and 4), suggesting that desflurane may produce less depression of sympathetic tone and autonomic reflexes than isoflurane and therefore result in greater maintenance of mean arterial pressure and contractile function at similar levels of anesthetic depth. In general, desflurane also caused less cardiovascular depression than did equianesthetic concentrations of halothane or enflurane. Both desflurane and isoflurane also increased diastolic coronary blood flow velocity (measured with a Doppler ultrasonic flow transducer) and decreased diastolic coronary vascular resistance, indicating that desflurane, like isoflurane, but not halothane or enflurane, may produce coronary vasodilation. In contrast to isoflurane, when heart rate was prevented from increasing during autonomic nervous system blockade, desflurane caused no change in coronary flow.

Merin et al. (18), in a concurrent investigation, also examined the effects of desflurane and isoflurane on cardiovascular dynamics and regional blood flow in the chronically instrumented dog. They (18) demonstrated that desflurane and isoflurane produced nearly identical hemodynamic effects at several equianesthetic concentrations, including similar decreases in mean arterial pressure and myocardial contractility, as assessed by left ventricular peak positive dP/dt. These results were in contrast to the findings of Pagel et al. (17) in dogs but supported the observations of Weiskopf et al. (7,8,10,11) in swine. Merin et al. (18) also reported that desflurane and isoflurane produced similar increases in coronary blood flow and decreases in coronary vascular resistance. Desflurane maintained hepatic arterial flow (measured with a Doppler flow probe) and hepatic vascular resistance. In contrast, isoflurane produced an increase and decrease, respectively, in these variables. The combined total hepatic blood flow (portal plus hepatic arterial) was significantly decreased by desflurane at high concentrations, reflecting decreased portal flow. In contrast, total hepatic blood flow was unchanged by isoflurane. Neither desflurane nor isoflurane significantly affected renal blood flow; calculated renal vascular resistance was decreased by both anesthetics. The effects of desflurane on hepatic and renal perfusion have also been recently examined in our laboratory with use of radiolabeled microspheres (J. C. Hartman et al., unpublished data). Preliminary findings of this investigation support those reported by Merin et al. (18).

Because desflurane may produce mild coronary vasodilation similar to isoflurane, the theoretical potential exists for this new anesthetic to produce redistribution of coronary collateral blood flow away from ischemic myocardium ("coronary steal") during an increase in blood flow to normal zones (19). Hartman et al. (20) studied the effects of desflurane on regional distribution of myocardial blood flow (by the radioactive microsphere technique) in a chronically instrumented canine model of multivessel coronary artery disease. This investigation indicated that desflurane did not redistribute blood flow away from collateral-dependent myocardium to normal regions by a coronary steal mechanism when heart rate and mean arterial pressure were restored to postocclusion control levels (Figure 5). Similar results were obtained in previous investigations in this model with isoflurane (21,22) in direct contrast to use of adenosine, a potent coronary vasodilator that produces pronounced coronary steal despite correction of heart rate and mean arterial pressure to control values.

The effects of desflurane versus isoflurane on left ventricular mechanics during systole and diastole have been examined by Pagel et al. (23,24). Myocardial contractility was studied in chronically instrumented dogs with pharmacologic autonomic nervous system blockade (23). Contractility was evaluated by means of the preload recruitable stroke work versus

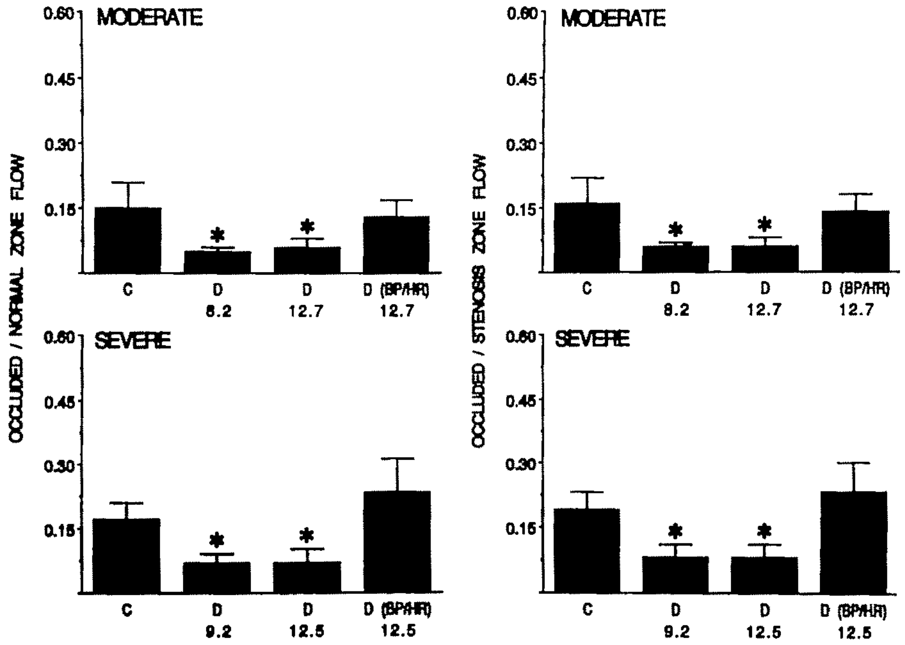

Figure 5. Occluded/normal zone (*left panels*) and occluded/stenotic zone (*right panels*) ratios of myocardial blood flow in chronically instrumented dogs with moderate (*top panels*) or severe (*bottom panels*) left circumflex coronary artery stenosis. Data obtained during conscious state (C), during two concentrations of desflurane (D), and with blood pressure and heart rate returned to levels present in conscious state (BP/HR) during high concentration of desflurane. *Significantly ($P < 0.05$) different from the conscious state. (Modified from original figures of Hartman et al. [20]. With permission from the International Anesthesia Research Society.)

end-diastolic segment length relationship, a linear and relatively afterload-insensitive extension of the Frank-Starling concept that has been shown to be a reliable index of inotropic state in conscious (25, 26) and anesthetized dogs (26). The preload recruitable stroke work versus end-diastolic segment length relationship was calculated from left ventricular pressure-segment-length loops generated by sequential constriction of the inferior vena cava with a hydraulic vascular occluder. The preload recruitable stroke work versus end-diastolic segment-length slope decreased similarly when equianesthetic concentrations of desflurane and isoflurane were administered, indicating equivalent direct decreases in myocardial contractility (Figure 6). Boban et al. (27), using isolated guinea pig hearts, recently demonstrated that desflurane and isoflurane produced similar degrees of myocardial depression in vitro.

The effects of desflurane, isoflurane, and halothane on left ventricular diastolic function in chronically instrumented dogs were also examined by Pagel et al. (24). Diastolic function has been shown to significantly influence systolic performance in several pathologic states, including ischemic heart disease, left ventricular hypertrophy, and cardiomyopathy (28–30). Using analysis of left ventricular pressure-segment-length loops, Pagel et al. (24) demonstrated that desflurane, isoflurane, and halothane prolonged isovolumetric relaxation to a similar extent, as evaluated with an invasively derived time constant of relaxation (Figure 7). In addition, although halothane impaired passive ventricular filling, desflurane and isoflurane had no effect on ventricular compliance (Figure 8). Thus, desflurane and isoflurane appeared to produce equivalent depression of ventricular function during diastole as well as systole.

In summary, although desflurane and isoflurane produce similar cardiovascular effects, some subtle differences between these agents were noted in experimental animals. Desflurane appeared to maintain mean arterial pressure to a greater degree than equianesthetic concentrations of isoflurane in some investigations (14,17). Isoflurane produced dose-related decreases in SVR consistent with peripheral vasodilation, but desflurane did not uniformly do so in acutely (14) and chronically instrumented dogs (17). Otherwise, the similarities in cardiovascular effects produced by these agents were striking (31). Desflurane and isoflurane produced nearly indistinguishable changes in systemic, coronary, renal, hepatic, and cerebral hemodynamics. Although desflurane may produce some degree of coronary vasodilation in dogs (17,18), no evidence of coronary steal was noted in a canine model of multivessel coronary artery disease (20). No differences between these agents were identified when left ventricular systolic and diastolic function were examined in vivo (23,24) and in vitro (27).

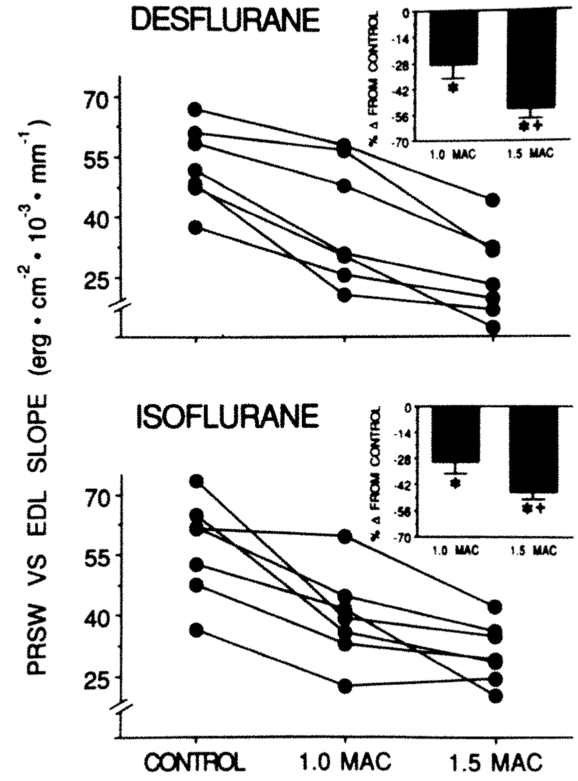

Figure 6. Preload recruitable stroke work (PRSW) versus end-diastolic segment length (EDL) slope for each chronically instrumented dog ($n = 7$) during conscious control and 1.0 and 1.5 MAC desflurane (*top panel*) and isoflurane (*bottom panel*). *Insets* depict data represented as percent change from control. *Significantly ($P < 0.05$) different from control. †Significantly ($P < 0.05$) different from 1.0 MAC. No differences were observed between desflurane and isoflurane groups at either anesthetic concentration. (Original figure from Pagel et al. [23]. Reproduced with permission of authors and publisher.)

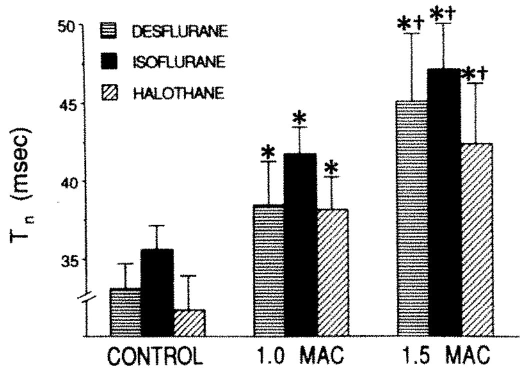

Figure 7. Histograms depicting effects of desflurane, isoflurane, and halothane on time constant of isovolumetric relaxation calculated assuming a nonzero asymptote of ventricular pressure decay (T_n) in chronically instrumented dogs with autonomic nervous system blockade. *Significantly ($P < 0.05$) different from the conscious control. †Significantly ($P < 0.05$) different from 1.0 MAC. No differences among desflurane, isoflurane, or halothane groups at either anesthetic concentration were observed. (Original figure from Pagel et al. [24]. Reproduced with permission of the authors and publisher.)

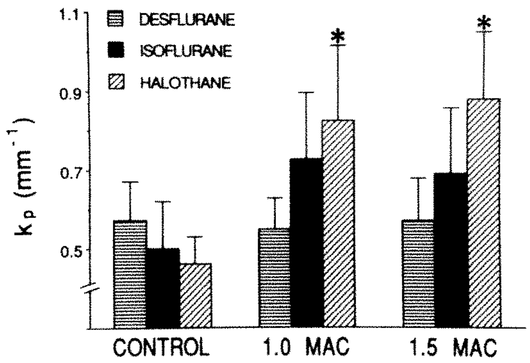

Figure 8. Histograms depicting effects of desflurane, isoflurane, and halothane on regional chamber stiffness (k_p, an index of ventricular compliance) in chronically instrumented dogs with autonomic nervous system blockade. *Significantly ($P < 0.05$) different from the conscious control. (Adapted from data of Pagel et al. [24]. With permission of authors and publisher.)

Cardiovascular Actions of Desflurane in Humans

Since the first report of the use of desflurane in humans by Jones et al. (32) in January 1990, numerous investigations have documented the hemodynamic effects of this new agent in a variety of clinical settings. Weiskopf et al. (33) studied the cardiovascular actions of desflurane in volunteers mechanically ventilated to maintain normocarbia. Desflurane caused dose-dependent decreases in mean arterial pressure and SVR and increases in right heart filling pressures and heart rate. These findings were similar to those described in earlier laboratory investigations from this group (7,8,10,11) and were also similar to the effects produced by isoflurane (Figure 9) when this agent underwent clinical trials (34). In addition, desflurane did not change cardiac index, left ventricular ejection fraction, or velocity of left ventricular circumferential fiber shortening (Vcfs), as assessed by echocardiography (Figure 10). These findings suggested that desflurane may produce less depression of myocardial contractility than other halogenated agents in humans. Mixed venous oxyhemoglobin saturation, oxygen consumption, and the ratio of oxygen transport to oxygen consumption remained constant in this study, indicating that desflurane maintained adequate tissue perfusion despite producing significant declines in perfusion pressure.

It has been established that duration of halothane and enflurane anesthesia affects hemodynamic profiles (35,36). Therefore, Weiskopf et al. (33) also studied the cardiovascular actions of desflurane after prolonged anesthesia (7 h). In general, prolonged anesthesia with desflurane resulted in less cardiovascular depression than during the first 90 min of anesthesia (33). Indices of cardiac filling, including

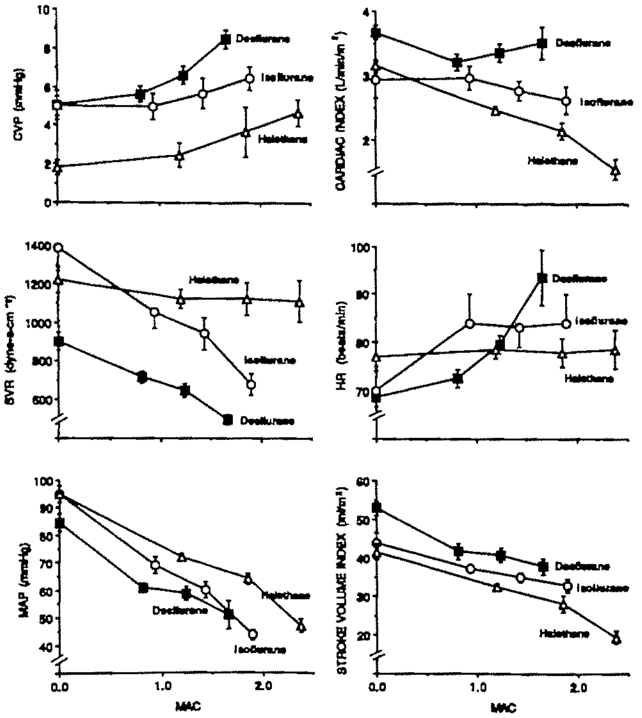

Figure 9. Central venous pressure (CVP), cardiac index, systemic vascular resistance (SVR), heart rate (HR), mean arterial pressure (MAP), and stroke volume index during conscious state (0 MAC) and during three steady-state concentrations of desflurane (33), isoflurane (34), and halothane (35) in three groups of healthy male volunteers. (Modified from original figure of Weiskopf et al. [33]. With permission from the International Anesthesia Research Society.)

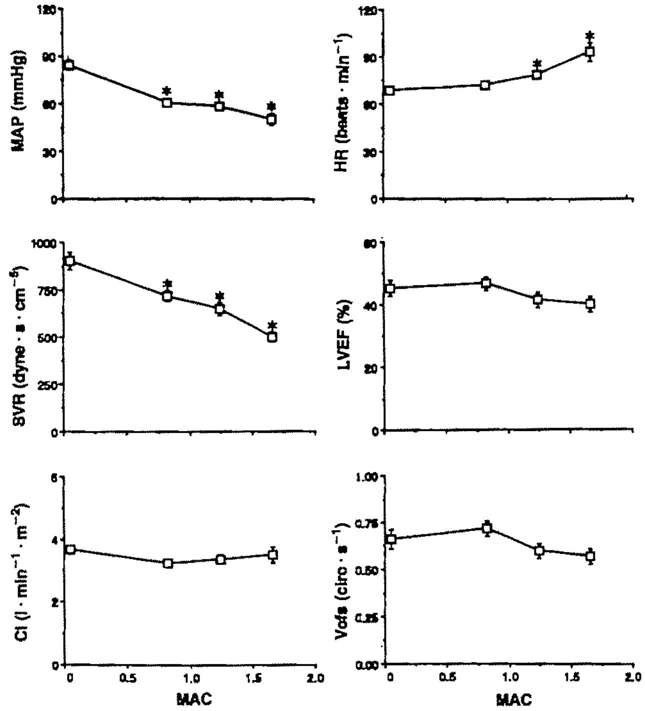

Figure 10. Mean arterial blood pressure (MAP), heart rate (HR), systemic vascular resistance (SVR), left ventricular ejection fraction (LVEF), cardiac index (CI), and velocity of left ventricular circumferential fiber shortening (Vcfs) during the conscious state (0 MAC) and during three steady-state concentrations of desflurane anesthesia in healthy male volunteers ($n = 12$). *Significantly ($P < 0.05$) different from conscious values. (Modified from original figures of Weiskopf et al. [33]. With permission from the International Anesthesia Research Society.)

central venous pressure and left ventricular cross-sectional area (as assessed by echocardiography), did not differ between the early and late periods at either 0.83 or 1.66 MAC desflurane. In contrast, heart rate and cardiac index were higher after prolonged anesthetic exposure at both concentrations than during the first 90 min. Other variables, including left ventricular ejection fraction, Vcfs, and skeletal muscle blood flow, did not change during prolonged anesthesia. No detrimental changes in peripheral tissue perfusion or oxygen consumption were identified as functions of duration of desflurane anesthesia.

The hemodynamic effects of combined desflurane and nitrous oxide anesthesia were studied in male volunteers by Cahalan et al. (37). Desflurane-nitrous oxide anesthesia caused dose-dependent decreases in mean arterial pressure, cardiac index, SVR, and left ventricular stroke work index (Figure 11), plus increases in pulmonary arterial and central venous pressures. No significant changes in heart rate were observed when desflurane was combined with nitrous oxide (Figure 11). The combination of these two agents also modestly increased left ventricular end-diastolic cross-sectional area and decreased Vcfs, systolic wall stress, and left ventricular ejection fraction, indicating myocardial depression. These authors also studied the effects of desflurane and nitrous oxide after prolonged anesthetic administration and, as in the previous investigation (33), found somewhat less cardiovascular depression after prolonged exposure. No evidence of circulatory insufficiency was found in any volunteer at any time. In addition, no segmental left ventricular wall motion abnormalities, ST-segment changes, or cardiac arrhythmias developed during administration of desflurane-nitrous oxide anesthesia, indicating that this combination probably did not cause myocardial ischemia in normal subjects.

The cardiovascular actions of desflurane with and without nitrous oxide during spontaneous ventilation were also studied in male volunteers by Weiskopf et al. (38). Desflurane anesthesia (in the presence and absence of nitrous oxide) decreased minute ventilation, increased carbon dioxide partial pressure, and produced somewhat different cardiovascular effects than those previously described (33,37). Desflurane alone caused decreased mean arterial pressure and SVR as well as increased heart rate, cardiac index,

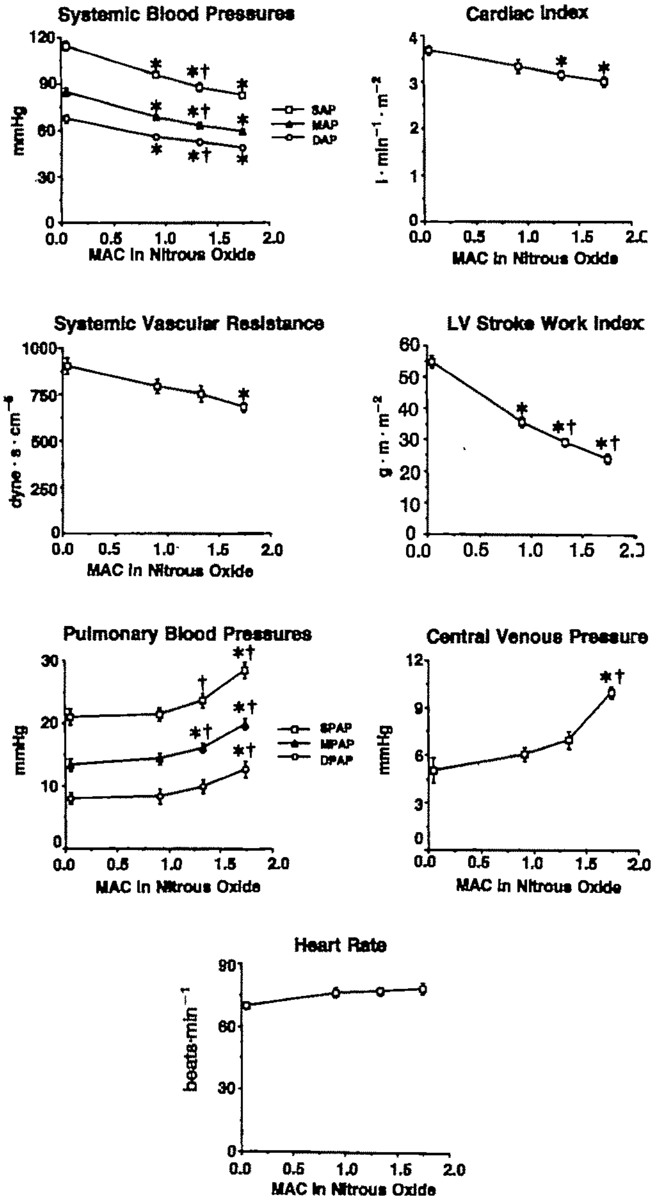

Figure 11. Systemic blood pressures, systemic vascular resistance, cardiac index, left ventricular (LV) stroke work index, pulmonary arterial pressures, central venous pressure, and heart rate in healthy volunteers in the conscious state and during three steady-state concentrations of desflurane-nitrous oxide anesthesia. *Significantly ($P < 0.05$) different from conscious values. †Significantly ($P < 0.05$) different when compared with previous levels of anesthesia. (Modified from original figures of Cahalan et al. [57]. With permission from the International Anesthesia Research Society.)

and central venous pressure. Left ventricular ejection fraction and Vcfs increased when desflurane was administered alone but did not change when desflurane was combined with nitrous oxide. Administration of desflurane to spontaneously breathing volunteers also produced increases in oxygen transport, the ratio of oxygen transport to oxygen consumption, mixed venous partial pressure of oxygen, and venous oxyhemoglobin saturation, indicating enhanced tissue oxygen delivery and maintenance of adequate tissue perfusion. The cardiovascular changes produced by desflurane with and without nitrous oxide during spontaneous ventilation differed from those observed during controlled ventilation. Increased cardiac index, central venous pressure, left ventricular ejection fraction, Vcfs, oxygen transport, and the ratio of oxygen transport to oxygen consumption increased in spontaneously breathing volunteers, in contrast to results obtained when ventilation was controlled (37). These findings can be attributed to direct desflurane-induced cardiovascular depression plus indirect hypercarbia-induced sympathetic stimulation. Differences in hemodynamic effects produced by desflurane during spontaneous versus controlled ventilation were also similar to those previously observed with isoflurane (39).

Cardiovascular responses to tetanic ulnar nerve stimulation were investigated in male volunteers during desflurane anesthesia by Yasuda et al. (40). Ulnar nerve stimulation produced increases in heart rate, mean arterial pressure, cardiac output, and pulmonary arterial pressures at 0.8 and 1.2 MAC desflurane. These hemodynamic responses were attenuated at 1.66 MAC. Desflurane and nitrous oxide produced attenuation of the peak response of heart rate and cardiac output but not mean arterial pressure. These results were consistent with previous findings for enflurane but not for halothane or an anesthetic that incorporated nitrous oxide and opioids (41).

Several investigations have been undertaken to determine the efficacy and safety of desflurane in patients with coronary artery disease. Thomson et al. (42) directly compared desflurane with isoflurane in patients undergoing coronary artery bypass graft surgery. After anesthetic induction with thiopental and fentanyl, desflurane or isoflurane was administered to maintain systolic blood pressure within 70%–100% and heart rate <120% of preanesthetic levels. Vasoactive drugs or additional fentanyl was used to control hemodynamics if end-tidal anesthetic concentrations between 0 and 2 MAC could not maintain hemodynamics within these predefined limits. The cardiovascular actions of desflurane and isoflurane before cardiopulmonary bypass were very similar (Figure 12). In addition, anesthetic requirements needed to maintain stable hemodynamics were indistinguishable between desflurane and isoflurane groups. During stressful stimuli (e.g., intubation or sternotomy), systolic pressure increased significantly more during isoflurane than during desflurane anesthesia. No differences in the incidence of electrocardiographic changes indicative of myocardial ischemia before cardiopulmonary bypass, perioperative myo-

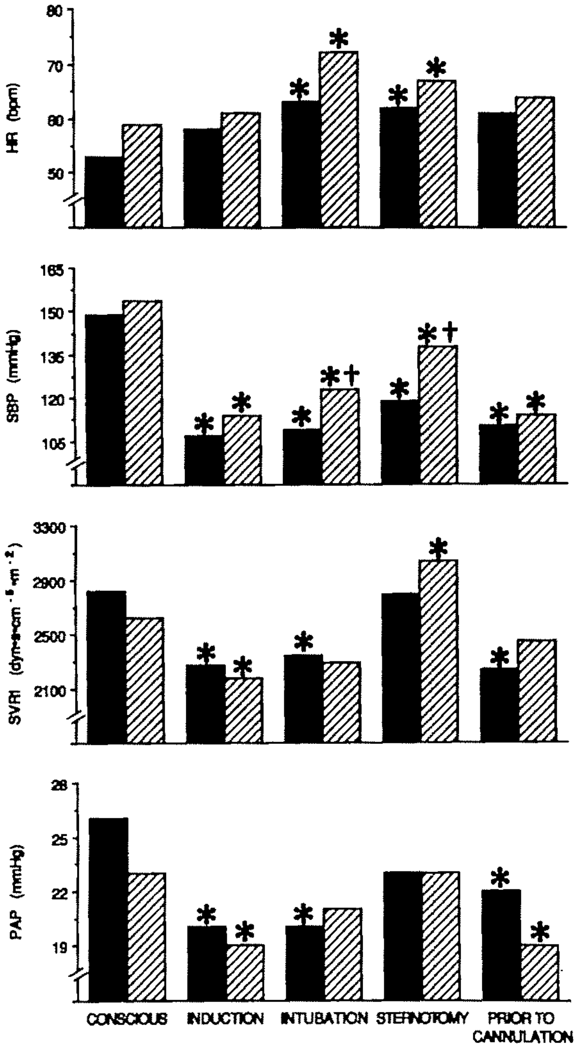

Figure 12. Heart rate (HR), systolic blood pressure (SBP), systemic vascular resistance index (SVRI), and pulmonary arterial pressure (PAP) in two groups of patients anesthetized with either desflurane (*solid bars*) or isoflurane (*hatched bars*) undergoing elective coronary artery bypass surgery. *Significantly ($P < 0.00083$) different from conscious values. †Significant ($P < 0.0071$) difference between groups. (Modified from data of Thomson et al. [42]. With permission of authors and publisher.)

cardial infarction, or perioperative mortality were identified between desflurane and isoflurane groups.

Helman et al. (43) also examined the impact of desflurane in patients with coronary artery disease by comparing the risk of myocardial ischemia during desflurane versus sufentanil anesthesia. Myocardial ischemia was detected by continuous Holter electrocardiography (before, during, and 48 h after surgery) and echocardiography (two-dimensional precordial and transesophageal before and after induction of anesthesia, respectively) during strict control of systemic hemodynamics in patients undergoing elective coronary artery bypass graft surgery. The authors reported that hemodynamic profiles produced by desflurane and sufentanil were similar. A trend toward increased incidence of ischemia detected by electrocardiographic changes and regional wall motion abnormalities occurred in the desflurane group in the induction period during increases in heart rate and arterial pressure. Desflurane was considered satisfactory for maintenance, during which hemodynamics were generally well controlled by desflurane and risk of ischemic events was not significantly increased. No differences between desflurane and sufentanil were identified when adverse cardiac outcome (ventricular failure requiring intraaortic balloon pump placement, myocardial infarction, or cardiac death) was considered. They suggested that myocardial ischemia risk was not increased with desflurane anesthesia compared with sufentanil anesthesia if hemodynamic variables were carefully controlled.

Desflurane and isoflurane were also studied in patients undergoing coronary artery bypass graft surgery by Ross et al. (44). Similar changes in systemic hemodynamics during induction, endotracheal intubation, skin incision, sternotomy, and prebypass and postbypass periods and at the end of surgery occurred during desflurane or isoflurane anesthesia. Isoflurane did produce significant declines in mean pulmonary artery and pulmonary capillary wedge pressures compared with desflurane at the end of induction. These results may indirectly indicate that desflurane produced greater cardiac depression during the early periods of anesthesia, perhaps because it equilibrated more rapidly than isoflurane. No changes in pulmonary artery pressures were observed at subsequent periods. Spiess et al. (45) also found desflurane and isoflurane to produce nearly identical hemodynamic actions before and after cardiopulmonary bypass when the concentration of either agent was adjusted to maintain surgical anesthesia.

T. K. Rao et al. (unpublished data) compared desflurane and isoflurane in patients undergoing repair of abdominal aortic aneurysms. These patients may be at risk for myocardial ischemia because of a high incidence of concomitant coronary artery disease. Isoflurane and desflurane produced nearly identical hemodynamic actions in this population. ST-segment changes and perioperative cardiovascular morbidity incidence was equivalent between the two anesthetic groups (T. K. Rao, unpublished data). These findings suggest that desflurane may be safe for patients undergoing abdominal aortic aneurysm resection.

Because desflurane has very low blood- and tissue-gas partition coefficients (1,2), it may be useful for rapid inhalation induction (although airway irritation may limit efficacy) and decreased emergence time after anesthesia, especially in outpatients (46–49).

Van Hemelrijck et al. (46) reported that the combination of desflurane and nitrous oxide produced changes in heart rate and systolic blood pressure similar to those produced by propofol and nitrous oxide in patients undergoing outpatient laparoscopy. Ghouri et al. (47) studied the recovery profile after desflurane-nitrous oxide versus isoflurane-nitrous oxide in outpatients. These authors reported equal numbers of adverse intraoperative cardiovascular events (defined as change in heart rate or blood pressure >20% of preinduction baseline value) between anesthetic groups. Azad et al. (50) found that equianesthetic end-tidal concentrations of desflurane and isoflurane (1.7 MAC) produced similar changes in heart rate and systolic and diastolic blood pressure when administered before and immediately after endotracheal intubation in outpatients. Excellent intubating conditions without neuromuscular blockers were reported with both anesthetics (50). The cardiovascular actions of desflurane were also studied in outpatients by Fletcher et al. (51). Inhalation induction with desflurane produced increased heart rate and systolic blood pressure similar to that caused by intravenous induction with thiopental. When isoflurane and desflurane were combined with nitrous oxide, similar hemodynamic profiles were present immediately before incision and in the first 5 min after beginning surgery. Both desflurane and isoflurane effectively blunted hemodynamic responses to surgical incision when administered at 1.3 MAC. In summary, a growing body of evidence supports the contention that desflurane produces systemic hemodynamic effects very similar to those produced by isoflurane in outpatients undergoing brief surgical procedures.

Preliminary investigations have reported cardiovascular effects of desflurane in other groups. Bartkowski et al. (52) studied systemic hemodynamics before surgical stimulation and found that desflurane produced a hemodynamic response identical to isoflurane. Similar alterations in systemic hemodynamics were also observed when desflurane and isoflurane were administered to elderly patients in a study by McMillan et al. (53). Use of opioids to treat intraoperative hypertension and tachycardia was greater with isoflurane than with desflurane in this investigation (53). This may indicate that desflurane produces greater (or quicker) suppression of sympathetic responses to surgical stimulation than does isoflurane. This conclusion must be qualified, because equianesthetic concentrations of desflurane and isoflurane were not administered (53). Battito et al. (54) also showed that desflurane and isoflurane produced similar hemodynamic effects in surgical patients. The cardiovascular responses to desflurane anesthesia in infants and children were studied by Taylor and Lerman (55). Desflurane decreased systolic arterial pressure before and after skin incision, but no significant changes in heart rate were observed. The authors concluded that desflurane produced stable hemodynamics when used as an induction agent and as a maintenance agent with nitrous oxide in infants and children (55).

Respiratory Effects of Desflurane

The capacity of desflurane to alter spontaneous ventilation has been noted in experimental animals. In pigs anesthetized with desflurane, normocarbia is maintained up to 1.2 MAC, but apnea occurs at end-tidal anesthetic concentrations between 1.2 and 1.6 MAC. Isoflurane produced similar respiratory depression, although the apneic threshold (defined as absence of ventilation for 1 min) for isoflurane was >1.6 MAC, in contrast to desflurane (I. J. Rampil et al., unpublished data). The apneic threshold in dogs anesthetized with desflurane was also slightly less than with isoflurane (2.38 vs 2.5 MAC) (Anaquest, unpublished data).

Lockhart et al. (56) described desflurane-induced depression of spontaneous ventilation with and without nitrous oxide in humans. Desflurane produced dose-dependent decreases in tidal volume and increases in respiratory rate (Figure 13) and depressed the ventilatory response to carbon dioxide in dose-related fashion with and without nitrous oxide. Arterial CO_2 tension (Pa_{CO_2}) increased with depth of anesthesia in both groups. The Pa_{CO_2} was significantly higher with desflurane alone than with desflurane plus nitrous oxide at 1.24 and 1.66 MAC. Minute ventilation decreased only at the highest level (1.66 MAC) of anesthesia with desflurane alone, and apnea occurred in two patients at an end-tidal concentration of 12%. The ratio of dead-space ventilation to tidal ventilation (V_D/V_T) and intrapulmonary shunt fraction ($\dot{Q}s/\dot{Q}t$) increased in dose-related fashion with desflurane with and without nitrous oxide.

Lockhart et al. (56) indicated that desflurane was a ventilatory depressant and that its effect on ventilation was comparable to that of other inhaled anesthetics (57,58). With deeper anesthesia, depression of ventilation observed with desflurane was most comparable to that previously reported for enflurane (57) (i.e., was greater than that previously reported for isoflurane [58]).

The low solubility of desflurane has stimulated interest in the potential of this agent for inhalation induction. Van Hemelrijck et al. (46) described a high incidence of breath holding, apnea, and coughing during inhalation induction with desflurane. Oral secretions were a problem in three patients who had

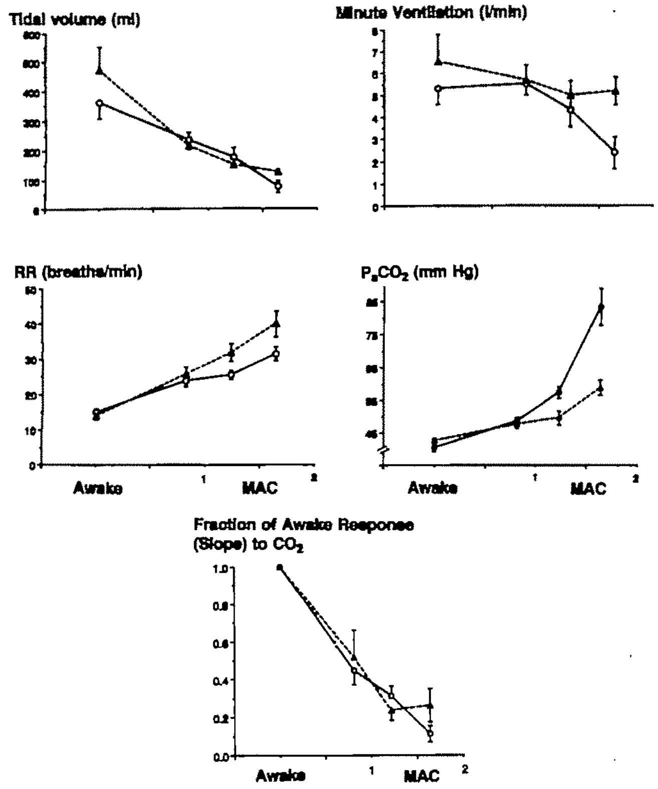

Figure 13. Effects of three steady-state concentrations of desflurane on tidal volume, respiratory rate (RR), minute ventilation, arterial carbon dioxide tension ($Paco_2$), and response to CO_2 in the presence (*solid triangles*) and absence (*open circles*) of 60% nitrous oxide in healthy male volunteers. (Modified from original figures of Lockhart et al. [56]. With permission of authors and publisher.)

anesthesia induced with desflurane, suggesting that this agent was a respiratory irritant. Rampil et al. (59) reported that 61% of patients had secretions requiring suction in a study of the effects of age or nitrous oxide on desflurane MAC. In addition, 50% of patients had persistent coughing, 34% manifested partial laryngospasm, and 29% exhibited breath-holding behavior (59). Incidence of these effects did not differ in the presence of nitrous oxide. Welborn et al. (60) also reported increased coughing, breath holding, and secretions during inhalation induction with desflurane compared with halothane in pediatric ambulatory patients. Therefore, although desflurane possesses biophysical characteristics advantageous for use as an inhalation induction agent, its airway irritability may limit the rate at which this volatile anesthetic can be delivered. Premedication with midazolam or fentanyl or a single-breath induction technique may improve patient tolerance to, and decrease airway irritability during, inhalation induction (61,62).

Conclusions

The investigations completed to date have shown that desflurane produces a systemic hemodynamic profile in volunteers and patients almost indistinguishable from its structural analogue isoflurane. No significant differences between the cardiovascular actions of desflurane and isoflurane were identified in volunteers during spontaneous and controlled ventilation with and without nitrous oxide. No evidence of desflurane-induced myocardial ischemia or desflurane-mediated increases in cardiovascular morbidity in patients with coronary artery disease have been demonstrated. Desflurane and isoflurane also produce similar hemodynamic effects during induction and maintenance of anesthesia in outpatients and pediatric and geriatric patients during a variety of surgical procedures. Rapid changes in anesthetic depth are easier to produce and may allow prevention or rapid treatment of hemodynamic alterations.

Desflurane produces depression of ventilation in experimental animals and in humans. Like isoflurane, desflurane also appears to be a mild respiratory irritant. Because only a limited number of studies have been performed to date examining the effects of desflurane on respiration, no firm conclusions with regard to the relative actions of desflurane and isoflurane on respiration can be established at present.

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DISCUSSION

DR. EUGENE ORNSTEIN (New York): As part of the study we performed, we have had patients who were given 1 MAC desflurane and oxygen for 30–45 min, after which the concentration of desflurane was increased to 1.5 MAC. This was without surgery, and we were very impressed with the transient responses in both heart rate and blood pressure. These patients were presumably fully anesthetized; yet they had significant heart rate and blood pressure increases. I was wondering if the San Francisco group found these transients?

DR. DAVID C. WARLTIER (Milwaukee): What was your initial concentration before jumping to 1.5 MAC, Dr. Weiskopf?

DR. RICHARD WEISKOPF (San Francisco): One MAC. In our human volunteer studies, we did see occasional transients (i.e., changes in heart rate) as we went from one concentration to another, but they were transient. We did not consider that to be a potential problem, so we did not study that in any sort of prospective manner. I cannot really make any further comment on it other than we did see it from time to time.

DR. BEVERLY PHILIP (Boston): What about the induction period before steady state? What cardiovascular changes were seen even if they are not being reported here from the investigative groups? My question concerns both the volunteers who had less premedication and the surgical patients. I am also asking what fentanyl dose these patients might have had to cause a difference, if there was one.

DR. WARLTIER: We have limited experience with this, but if you do an inhalation induction, during induction you will see hypertension and tachycardia. This can be blunted significantly by pretreatment with either thiopental or fentanyl.

DR. JACQUELINE M. LEUNG (San Francisco): One of the peculiar effects of desflurane that has not really been mentioned here yet is the seemingly biphasic effect on hemodynamics. That is, induction and maintenance seem somewhat different. Our experience in our 200-patient study, where half of the patients received desflurane, demonstrated that despite the fact that patients were receiving controlled ventilation and had no apparent airway irritation and no signs of excitement, there were nonetheless significant increases in *pulmonary* blood pressure. Pulmonary wedge pressure increased by an average of 50% and pulmonary artery diastolic pressure by an average of 100%. Systemic systolic pressures increased an average of 20%. I should say that in these patients, >50% required esmolol to control their systemic and pulmonary blood pressures.

DR. RONALD D. MILLER (San Francisco): Is this during an inhalation induction?

DR. LEUNG: We quickly abandoned inhalation induction after the first few patients. We used a sleep dose of thiopental, breathed them down if you will, titrated in the muscle relaxant, and then incrementally increased the desflurane concentration as per protocol. We wanted to uncover the coronary effects of this drug, so we did not use any prophylactic narcotic as a lot of studies had done and as we previously did in another study using isoflurane, where we used fentanyl as an adjuvant. I should also mention that differences in myocardial ischemia were seen primarily during induction, detected only by two sensitive continuous modalities of measurement, namely, Holter monitoring and transthoracic echo.

DR. R. D. MILLER: What did you mean by differences in myocardial ischemia? Different between what and what?

DR. LEUNG: The difference between desflurane anesthesia and the control group given high-dose sufentanil.

DR. WARLTIER: I think that is what we would expect; namely, better control of hemodynamics with sufentanil than with desflurane. What MAC were you using?

DR. LEUNG: Our mean end-tidal concentration of desflurane on induction was approximately 10%.

DR. WARLTIER: I think that is to be expected and goes back to the use of adjuncts with desflurane for control of systemic hemodynamics. Of course, hypertension and tachycardia are ordinarily seen on induction in experimental animals and are totally eliminated by autonomic nervous system blockade.

DR. WEISKOPF: A question for Dr. Leung. When you saw what looked like sympathetic stimulation during induction, approximately what was the end-tidal concentration of desflurane?

DR. LEUNG: I'll defer to Dr. Helman.

DR. JAMES HELMAN (San Francisco): As we got above 6%–7% desflurane, with continued increments, the hemodynamics continued to increase with almost a linear relationship.

DR. WEISKOPF: At some point that stimulation defervesced. What was the range where you saw the stimulation and when did it go away?

DR. HELMAN: It actually did not spontaneously defervesce. Our study design was to keep systolic blood pressure within <120% of its ward control and to maintain a heart rate of <120%. We therefore treated the stimulation with esmolol or nitroprusside, or both. It actually did not abate until after the patient was tracheally intubated.

DR. WEISKOPF: At what concentrations?

DR. HELMAN: An end-tidal concentration of 10%. Some patients required an end-tidal concentration of up to 16%–17%.

DR. WARLTIER: One of the things that is very interesting about that is that the stimulation is reflected not just in heart rate, but also in systolic blood pressure as well. It is not simply a baroreflex, for example, a decrease in systolic pressure causing a reflex increase in heart rate by an agent that might affect the autonomic nervous system less than another agent. This is something different from that and also different from isoflurane, I agree.

DR. WEISKOPF: One of the major differences between the Helman-Leung study and other studies is that Drs. Helman and Leung used an almost pure inhaled anesthetic for those coronary bypass patients. This is not what we would usually do clinically. A question I would like to ask Dr. Warltier is, from what you have summarized very nicely, would you expect that desflurane would probably be a negative inotropic drug in patients with heart failure, with preexisting cardiac disease?

DR. WARLTIER: Absolutely, no question about it. Just like any volatile anesthetic would be, this drug is a negative inotrope.

DR. WEISKOPF: Even though it looks like it supports circulation a little better in healthy patients than isoflurane, we would not expect that to be true in the patient we are talking about, would we?

DR. WARLTIER: If we are talking about a patient with heart failure who has a higher sympathetic tone to begin with, this drug may not increase sympathetic tone more than that. Instead, you will see its direct effects, and so I would expect it would exacerbate heart failure much like any other volatile anesthetic.

DR. RICHARD M. SMILEY (New York): With regard to the discussion we are having about excitement or sympathetic overactivity, I think we should keep in mind that all volatile anesthetics probably, or even definitely, have a period of excitement associated with their onset, and that some of the differences we are talking about may be due to kinetic differences in the onset of these drugs. There may conceivably be some difference in which centers are first anesthetized, perhaps some inhibitory centers.

DR. MICHAEL DAMASK (New Jersey): Looking at 60 patients undergoing triple A resections, all had a significant amount of fentanyl preoperatively, up to 10 μg/kg, and the differences that Drs. Helman and Leung brought out in terms of ischemia, increased heart rate, and increased pulmonary pressures were not seen in these other studies. In the large multicenter program in which researchers looked at ASA physical status III and IV patients, the cardiovascular differences between isoflurane and desflurane were really not clinically significant at the time points at which data were recorded.

DR. ROBERT HUDSON (Winnipeg): Just some comments on our own study: I would not want anyone to draw the conclusion from our data that the small dose of thiopental we used (approximately 2 mg/kg) and a somewhat larger dose of fentanyl (approximately 10 μg/kg) necessarily changed the intrinsic cardiovascular response to either desflurane or isoflurane. We have seen in the studies that were just reviewed that the problems, if that's what they are, with desflurane tend to occur at fairly high concentrations, >1.2 MAC or so, particularly with increases in heart rate. In our clinical study, we did not really get up to those concentrations because we did not need them to maintain blood pressure within our stated ranges. We therefore have not tested the hypothesis that pretreatment modifies the intrinsic response to a given concentration of desflurane or, in fact, isoflurane.

DR. WARLTIER: I agree. If this stimulation does occur at higher MAC levels it needs to be studied. In addition, we need to investigate directly, comparing desflurane to isoflurane, not to sufentanil in the same patient population at these higher MACs of volatile agents.

DR. KENNETH ZAHL (New York): There is always underlying concern about cardiovascular safety. But for the clinician, let's say you are doing a relatively straightforward case. You are not going to have pulmonary artery catheters or echocardiography. Often, you will have only a three-lead electrocardiogram. You have to get the patient anesthetized. The relevant question is whether or not you can safely overpressure the patient with 2 or 3 MAC like you can with enflurane, isoflurane, or halothane? There are many patients who will not be heavily monitored and who will have only peripheral blood pressure cuffs and pulse oximeters. In the chronically instrumented dog, you have a preparation where you are blocking any potential beta stimulation. If there is a beta-stimulation mechanism involved (i.e., sympathetic stimulation), could you design another protocol to detect that? Maybe to obtain, not necessarily coronary steal, but other myocardial variables of ischemic propensity with higher doses of desflurane in the chronically instrumented dog.

DR. WARLTIER: We studied desflurane in the absence versus the presence of autonomic nervous system blockade in dogs. There is certainly no direct beta stimulation by any volatile anesthetic. That is also easy to show in isolated tissue preparations, which is the classic way to show beta-agonist-type activity. We have always believed that, at least in the dog, desflurane seems to interfere with autonomic reflexes to a lesser extent than the other volatile agents, although I really do not have a solid basis for that other than just seeing what happens during induction and heart rates in comparison to arterial pressures at the various MAC levels.

DR. WEISKOPF: I guess I still fail to understand the difference between Drs. Leung and Mangano's study and the results in our volunteers, in that at approximately 10%, which is roughly 1.4–1.5 MAC end-tidal concentration, they saw cardiovascular stimulation, whereas in our volunteers we did not. Obviously, there is a disparity for which I do not have an answer.

Effects of Desflurane on the Central Nervous System

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Desflurane causes dose-dependent decreases in cerebrovascular resistance and cerebral metabolic rate of oxygen consumption ($CMRo_2$), suggesting that desflurane is a cerebral arteriolar dilator with global flow-metabolism coupling similar to halothane and isoflurane. Desflurane is also similar to isoflurane in that cerebrovascular responsivity to carbon dioxide appears to be maintained. In the dog, arterial hypotension to 40 mm Hg induced with 2.4 MAC desflurane resulted in global decreases in cerebral blood flow of 60% and $CMRo_2$ of 20%. Concentrations of cerebral metabolites of high-energy phosphates were not significantly deranged. The intracranial pressure data from humans are controversial. Desflurane and oxygen at 1 MAC caused sustained increases in cerebrospinal fluid pressure (maximum of 19 ± 6 mm Hg) in patients undergoing craniotomy for mass lesion despite prior establishment of hypocapnia. In a more recent study, the same investigators reported similar cerebrospinal fluid pressures before and after 0.5 MAC of either isoflurane or desflurane in 50% N_2O. The electroencephalographic effects of desflurane are similar to those of isoflurane in humans, and burst suppression is easily achieved. There are no data available concerning possible interactions between desflurane and the outcome of a cerebral ischemic event. Similar to other potent volatile agents, desflurane can cause cerebral vasodilation and may result in intracranial pressure changes in vulnerable patients, but if adequate hyperventilation and depth of anesthesia are maintained, it is probably safe to use desflurane in a manner similar to isoflurane in patients with decreased intracranial compliance.

(Anesth Analg 1992;75:S32–7)

Relatively few studies have addressed the impact of desflurane on physiologic processes in the central nervous system; the available evidence points to a pattern of effects similar to that seen with isoflurane.

The most striking difference between desflurane and currently available potent agents is a more rapid cerebral washin and washout. This is predictable, based on the low solubility of the agent and has been elegantly confirmed by Lockhart et al. (1) using ^{19}F nuclear magnetic resonance spectroscopy. These authors utilized a 30-min washin and 120-min washout to examine cerebral (nuclear magnetic resonance) and alveolar (gas chromatography) concentrations. Desflurane exhibited faster elimination than did isoflurane and halothane. Hysteresis between alveolar and brain concentrations was similar for all three agents.

Effects on Cerebral Blood Flow and Metabolism

Desflurane's effects on cerebral blood flow (CBF) and cerebral metabolic rate for O_2 ($CMRo_2$) have been examined in dogs (2). Lutz et al. used the venous outflow CBF method and sagittal sinus sampling to determine the arteriovenous difference in O_2 content and examined the dose-response of desflurane at 0.5, 1.0, 1.5, and 2.0 MAC in six dogs (2). At higher MAC concentrations, arterial blood pressure support with phenylephrine was necessary to maintain constant values. Their results are summarized in Figure 1.

There was a dose-dependent decrease in cerebrovascular resistance regardless of arterial blood pressure support (Figure 1). With arterial blood pressure support, CBF increased at the two highest MAC multiples (Figure 2). Similar to other potent agents, this suggests that desflurane is a cerebral arteriolar dilator. The $CMRo_2$ progressively declined with increasing MAC (Figure 3), as is seen with isoflurane in this range (3,4). It seems reasonable to assume persistent global flow-metabolism coupling, as seen with halothane and isoflurane (5). Autoradiographic studies that document regional effects of desflurane on flow and metabolism patterns have not yet been reported.

Desflurane, as expected, maintains cerebrovascular responsivity to carbon dioxide ($CVRco_2$). Over the $Paco_2$ range of approximately 22–40 mm Hg, Lutz et al. (6) reported appropriate $CVRco_2$ at three MAC levels in dogs. In Figure 4, the 1 MAC values are compared with 1 MAC isoflurane in the dog for both venous outflow

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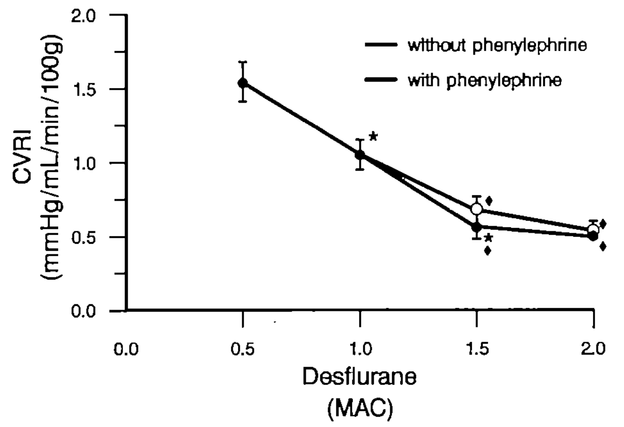

Figure 1. Effect of desflurane on cerebrovascular resistance index (CVRI). Desflurane produced a dose-dependent decrease that was unaffected by the phenylephrine infusion. Mean ± SE ($n = 6$). *Significantly different from value obtained at 0.5 MAC ($P < 0.05$). (♦) Significantly different from value obtained at 1.0 MAC ($P < 0.05$). (Data from Lutz et al. [2].)

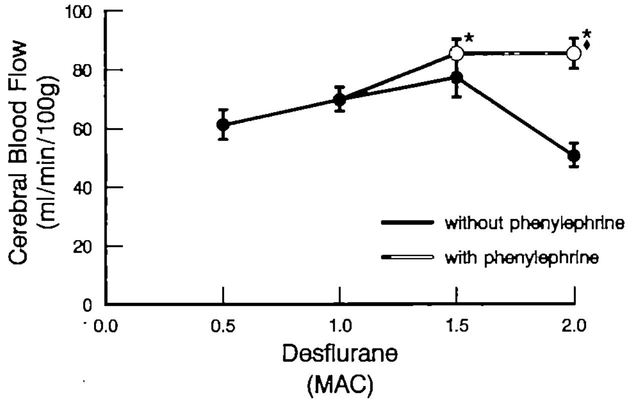

Figure 2. Effect of desflurane on cerebral blood flow. With blood plasma support, desflurane produced a dose-related increase in cerebral blood flow. Mean ± SE ($n = 6$). *Significantly different from value obtained at 0.5 MAC ($P < 0.05$). (♦) Significantly different from value obtained at 1.0 MAC ($P < 0.05$). (Data from Lutz et al. [2].)

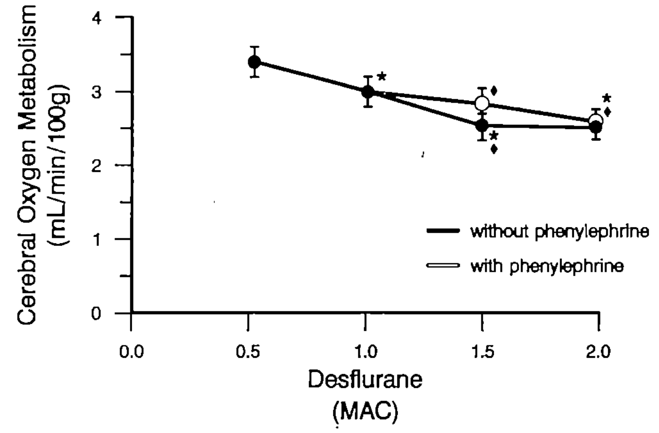

Figure 3. Effect of desflurane on cerebral metabolic rate for O_2 ($CMRo_2$). Desflurane produced a significant dose-related decrease in $CMRo_2$ from 0.5 to 2.0 MAC. Phenylephrine had no significant effect on $CMRo_2$. Mean ± SE ($n = 6$). *Significantly different from value obtained at 0.5 MAC ($P < 0.05$). (♦) Significantly different from value obtained at 1.0 MAC ($P < 0.05$). (Data from Lutz et al. [2].)

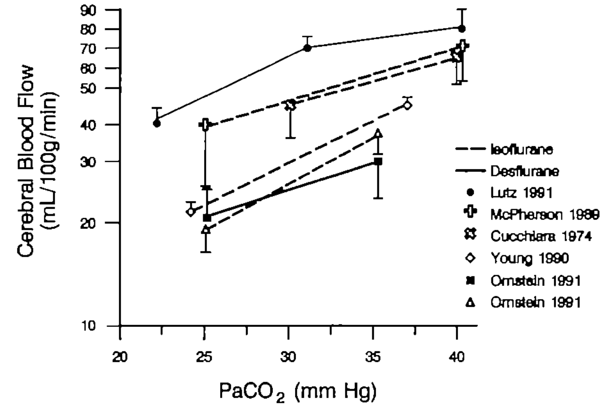

Figure 4. Comparison of cerebrovascular reactivity to carbon dioxide ($CVRco_2$) for isoflurane and desflurane. *Top three graphs*, animal studies; *bottom three graphs*, human studies. The $CVRco_2$ appears to be similar for both agents. (Animal data from Lutz et al. [6], Cucchiara et al. [7], and McPherson et al. [8]; human data from Young et al. [10] and Ornstein et al. [9].)

CBF methodology (7) and use of radiolabeled microspheres (8).

The only human CBF data currently available were reported by Ornstein et al. (9) who utilized intravenous ^{133}Xe. They compared desflurane and isoflurane on CBF at two concentrations (1.0 and 1.5 MAC) in an air/oxygen mixture during hypocapnia in 12 patients undergoing craniotomy for tumor. They also assessed $CVRco_2$ at 1.25 MAC. There was no difference between isoflurane and desflurane at the two different MAC levels (Figure 5), and $CVRco_2$ was similar for both (Figure 4). Desflurane's effect on human $CVRco_2$ (10) is similar to that reported for isoflurane (9).

Desflurane-Induced Hypotension

Milde and Milde (11) examined the systemic and cerebral effects of arterial hypotension induced with desflurane in 11 dogs (Figure 6). Baseline measurements were obtained at 1 MAC and hypotension to 50 mm Hg (2.2 MAC) and 40 mm Hg (2.4 MAC). At a 40%–50% decrease in cardiac index, there was approximately a 20% decrease in $CMRo_2$. The CBF decreased 36% and 60% at mean arterial pressures of 50 and 40 mm Hg, respectively. After hypotensive periods, cerebral metabolite concentrations of adenosine triphosphate, phosphocreatine, and lactate were within the range of normal canine values for their laboratory, although lactate was moderately increased. They concluded that there was adequate perfusion to maintain $CMRo_2$ during desflurane-induced hypotension. Desflurane appears similar to isoflurane (12) in that hypotension can be easily induced and maintained, as shown in Figure 6.

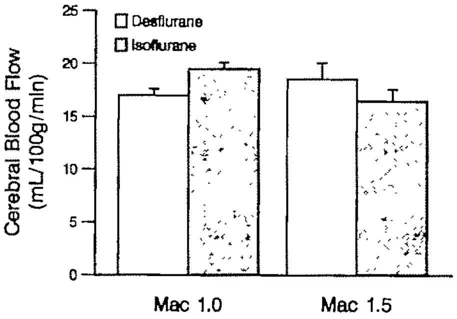

Figure 5. Cerebral blood flow dose-response for isoflurane (air/O_2) and desflurane (air/O_2). There was no difference between the two agents at either MAC level. (Data from Ornstein et al. [9].)

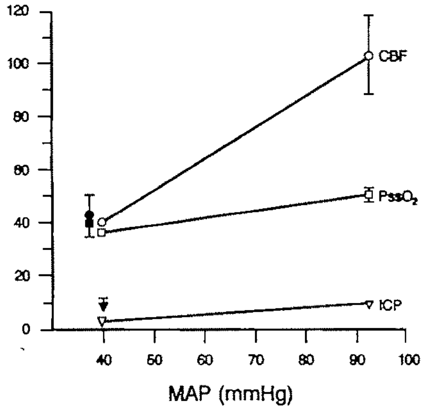

Figure 6. Cerebral effects of desflurane-induced hypotension in dogs. Changes in cerebral blood flow (mL·100 $g^{-1}·min^{-1}$), sagittal sinus O_2 tension ($PssO_2$, mm Hg), and intracranial pressure (ICP, mm Hg) are shown (*open symbols*). (Data from Milde and Milde [11]. Values are compared with data for isoflurane (*filled symbols*) at a similar level of hypotension from a previous study by Newberg et al. [12].)

Effects on Intracranial Pressure

In dogs without intracranial pathology, the aforementioned studies of Lutz et al. (2,6) and Milde and Milde (11) showed trivial effects on intracranial pressure (ICP). The data from Lutz et al. are summarized in Figure 7.

Data from humans with intracranial mass lesions are more controversial. Muzzi et al. (13) studied 10 patients with mass lesions who before induction of anesthesia underwent lumbar subarachnoid needle drainage that allowed measurement of lumbar cerebrospinal fluid pressures (LCSFP). There was no control group. Awake baseline LCSFP before induction of anesthesia was 11 ± 4 (mean ± SD) mm Hg. The LCSFP decreased after thiopental and showed variable increases after tracheal intubation. After 1 MAC desflurane was added (7.1% ± 0.6% in air/oxygen), sustained increases in LCSFP were observed in all patients until the dura was incised at $Paco_2$ of 26 ± 2 mm Hg. Maximal LCSFP at 45–75 min was 19 ± 6 ($P < 0.002$), range 13–33 mm Hg. The authors concluded that LCSFP increases after desflurane despite previous establishment of hypocapnia.

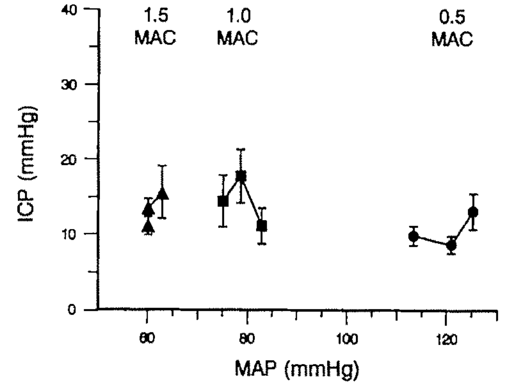

Figure 7. Intracranial pressure (ICP) response to three levels of desflurane at three levels of hypocapnia. Data points at each MAC level represent hypocapnia, normocapnia, and hypercapnia. Because of dose-related decreases in blood pressure, each of the three levels of hypocapnia, normocapnia, and hypercapnia are plotted as a function of mean arterial pressure (MAP). There were no differences at any level of desflurane or $Paco_2$. (Data from Lutz et al. [6].)

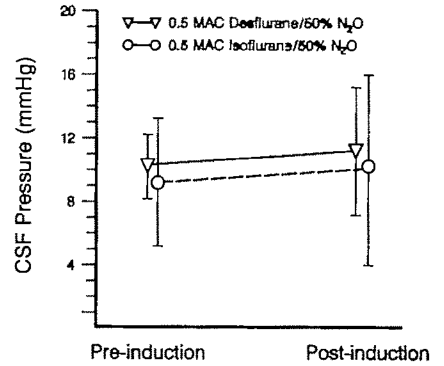

Figure 8. Effect of anesthetic induction on cerebrospinal fluid (CSF) pressure with isoflurane or desflurane in the presence of N_2O. There was no difference between agents before or after induction. (Data from Muzzi et al. [14].)

In a more recent study using similar methodology, the same group reported LCSFP before and after 0.5 MAC of either isoflurane or desflurane in 50% N_2O (14). As shown in Figure 8, there was no appreciable change in LCSFP with either regimen.

It is difficult to reconcile these two clinical studies, except that the latter was done with N_2O and half as much desflurane. Because desflurane, similar to isoflurane, causes no change in CBF with MAC levels used clinically, it is possible that there is some effect of desflurane to increase cerebral blood volume, independent of its effect (or lack thereof) on cerebral arteriolar resistance, perhaps by venodilation. There is no clinical evidence that operative conditions are different with desflurane versus isoflurane (W. L. Young and E. Ornstein, unpublished observations, 1991).

There is one study in progress to attempt to sort out the issue of ICP increases. Preliminary observations suggest that addition of either isoflurane or desflurane

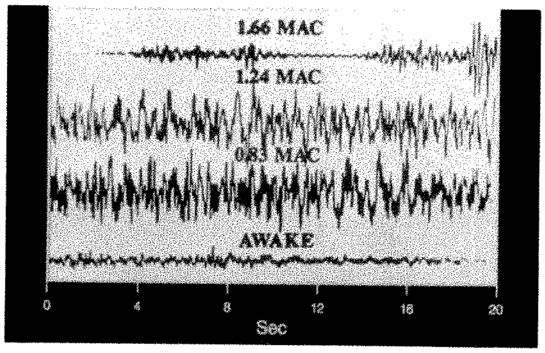

Figure 9. Human EEG during desflurane anesthesia. (The EEG patterns for desflurane in humans are strikingly similar to those of isoflurane.) (Data from Rampil et al. [17].)

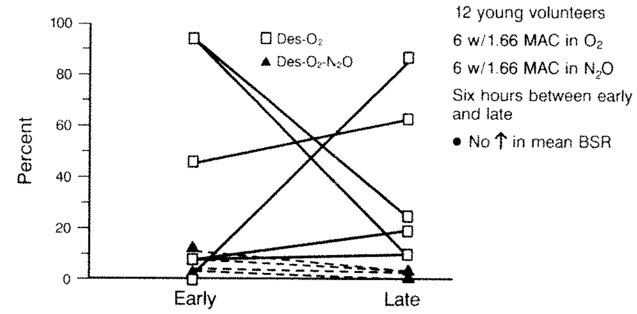

Figure 10. Burst suppression rate during desflurane (Des) anesthesia. No evidence for "EEG tolerance." (Data from Rampil et al. [17].)

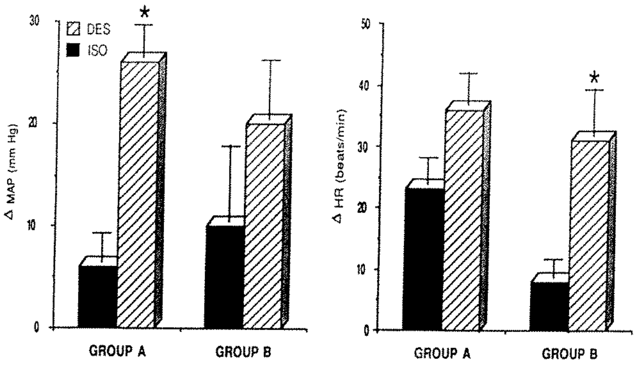

Figure 11. Systemic hemodynamic changes from preinduction to 5–6 min after induction. $^*P < 0.05$. Group A, nonneurosurgical patients from Smiley et al. (19); group B, neurosurgical patients from Ornstein et al. (9). There was a trend for desflurane (DES) patients to have more pronounced heart rate and blood pressure changes after induction (see text for further explanation). ISO, isoflurane. (Data from Fleischer et al. [20]).

(in oxygen) results in similar effects on LCSFP, although LCSFP increases are sometimes seen with either agent (Z. Ebrahim, personal communication, 1992).

Whatever the outcome of present and future studies, desflurane is clearly a potent cerebral vasodilator that must be used carefully in patients with decreased intracranial compliance. The net vasodilation of desflurane is, in a fashion similar to isoflurane, a balance between its direct dilating effects and the increase in vascular tone associated with its ability to suppress cerebral metabolic activity. Patients at greatest risk for increased ICP with desflurane might be those with the greatest previous depression of $CMRo_2$, as is the case for isoflurane (15).

Electroencephalographic Effects

In swine, Rampil et al. (16) demonstrated dose-related depression of electroencephalographic (EEG) activity up to and including burst suppression, comparable to effects seen with an equipotent dose of isoflurane. These authors further investigated the effects of 6%, 9%, and 12% desflurane (0.83, 1.24, and 1.66 MAC) in O_2 and 3%, 6%, and 9% desflurane in 60% N_2O in O_2 in 12 healthy human volunteers. They further studied hypercapnia and hypocapnia and attempted to provoke excitatory activity by loud handclapping (17). The EEG effects of desflurane were roughly similar to those of isoflurane in humans (Figure 9). There was no epileptiform activity. As in the swine model, desflurane significantly suppressed EEG activity; prominent burst suppression was observed at MAC levels >1.24. Addition of N_2O predictably lessened the depressant effect of desflurane on the EEG.

A topic of some controversy is the occurrence of EEG tolerance to the cerebral effects of desflurane. Lutz et al. (2) and Milde and Milde (11) reported EEG tolerance to desflurane, the animals progressing from relative EEG quiescence to more awake patterns over 30–60 min in their canine preparations despite constant $CMRo_2$ and anesthetic concentrations. In contrast, Rampil and colleagues (17,18) found no evidence of tolerance in either humans or swine. They contended that the nature of the EEG sampling (burst suppression being a nonstationary phenomenon) or interspecies differences, or both, probably account for the differing observations (Figure 10). Whatever the explanation, tolerance has not been shown to be an issue in humans.

Desflurane Use in the Neurosurgical Patient

As in other settings, the uptake and recovery characteristics of desflurane may offer advantages in neurosurgical patients in whom rapid differentiation of drug residua from operative sequelae is desirable at conclusion of surgery. Although rapid emergence has been demonstrated in nonneurosurgical patients (19), details of the clinical behavior of desflurane in the neurosurgical population have not yet been described.

Fleischer et al. (20) performed a retrospective review of hypertension and tachycardia during anesthetic induction in two separate randomized, open clinical studies (Figure 11). They analyzed systemic hemodynamic data for the initial 5–6 min of induction in 33 patients undergoing general anesthesia for surgery that did not include the thorax, abdomen, or central nervous system (19) and 16 patients undergoing elective craniotomy for mass lesions (9). At 5–6 min after induction (T5-6), mean arterial pressure elevated 28% from preinduction baseline was noted in nonneurosurgical desflurane patients versus 7% for the corresponding isoflurane patients ($P < 0.002$). Heart rate also increased almost uniformly (31 of 33 patients) in nonneurosurgical patients, but differences between those receiving desflurane versus isoflurane did not achieve significance ($P < 0.06$). In neurosurgical patients, the desflurane subset exhibited a 34% increase from baseline heart rate versus 11% for isoflurane. Mean arterial pressure elevation at T5-6 in neurosurgical patients was not statistically different between desflurane and isoflurane.

This study suggests that the use of desflurane as an agent in a combined intravenous and inhaled anesthetic induction without narcotic adjuvants may result in significant changes from baseline cardiovascular hemodynamics (i.e., mean arterial pressure and heart rate increases). These changes appear greater than those seen with isoflurane. Because tachycardia and hypertension may adversely impact patients with certain disease states (e.g., coronary artery disease or recently ruptured intracranial aneurysms), these findings should be borne in mind when planning anesthetic induction in such patients. The observed differences in the systemic hemodynamic effects of desflurane versus isoflurane warrant further investigation.

Summary and Conclusions

Cerebrovascular effects of desflurane appear similar to those of isoflurane in both normal subjects and in patients with intracranial mass lesions. There is dose-related depression of CBF, $CMRo_2$, and EEG activity. Desflurane may be used in a fashion similar to isoflurane to induce controlled hypotension. Use of desflurane during anesthetic induction may result in more pronounced arterial blood pressure and heart rate increases than isoflurane. These systemic hemodynamic changes are probably controllable with narcotics or other adjuvants.

Although definitive recommendations should await analysis of all available data, use of desflurane in the neurosurgical patient should be carefully considered. As is the case with isoflurane, use of desflurane may result in increases in brain volume or ICP in certain patients. Notwithstanding, if adequate hyperventilation and depth of anesthesia are maintained, it is probably safe to use desflurane in all but perhaps the most precarious cases of intracranial hypertension. Risks of increases in ICP should be weighed against the potential benefit of rapid emergence afforded by desflurane, particularly after prolonged or otherwise complicated neurosurgical procedures.

I thank Eugene Ornstein, PhD, MD, for his review of the manuscript and Joyce Ouchi for her assistance in manuscript preparation.

Addendum: Muzzi et al. have recently published their data as a full manuscript (Muzzi DA, Losasso TJ, Dietz NM, Faust RJ, Cucchiara RF, Milde LN. The effect of desflurane and isoflurane on cerebrospinal fluid pressure in humans with supratentorial mass lesions. Anesthesiology 1992;76:720–4). They added a nonrandomized and noncontemporaneous group of patients receiving equipotent isoflurane anesthesia. Desflurane CSFP became greater than the isoflurane group at 10 min after addition of the volatile anesthetic.

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DISCUSSION

DR. EDMOND I. EGER II (San Francisco): Do you have any explanation for the apparently increased intracranial pressure associated with desflurane in the earlier study done by the Mayo group?

DR. WILLIAM L. YOUNG (New York): I think it is plausible that their patients did have sustained increases in cerebrospinal fluid pressure. It probably had to do with their patient selection. They did not furnish a control group. The bottom line is that both agents [isoflurane and desflurane] can cause cerebrovascular relaxation. Patients at risk should be handled carefully with any inhaled agent.

DR. RICHARD M. SMILEY (New York): This question may be for Dr. Rampil as well as for Dr. Young. Is there anything from electroencephalographic (EEG) data to suggest that the kinetic differences between the drugs might lead to qualitative differences in the development of EEG changes? In other words, is there anything in the EEG data to suggest that the different speeds of uptake between isoflurane and desflurane into the brain resulted in qualitative differences in the EEG results you see, especially during times of changing concentration?

DR. IRA RAMPIL (San Francisco): I think the major problem lies with using the EEG as a measure of anesthetic effect. The EEG really reflects electrical activity in cortical pyramidal cells. Future studies should look at subcortical sites and see what is going on at different places in the brain.

DR. YOUNG: As far as the autonomic effects and their interaction with the cerebral effects, we previously did an autoradiographic study in rats comparing isoflurane and halothane, and we happened to look at the brainstem. It appears that isoflurane activates brainstem structures much more than halothane does. So perhaps if somebody looks, he or she might see that the differential effects of desflurane may even be greater than those of isoflurane.

DR. STEVEN ROBINSON (Portland): Is there any evidence that using desflurane allowed more rapid ability to evaluate the patient postoperatively or increased the ease of evaluating the patient postoperatively for neurologic deficits compared with isoflurane?

DR. YOUNG: There are no data. I think Dr. Ornstein and I both have the clinical impression that after a very long anesthetic patients who would have in the past been a little slow on the draw are pretty wide awake after a 12-h craniotomy, even when there has been considerable brain retraction. It would be difficult but useful to design a study to see whether, in fact, neurosurgical patients wake up faster, because there is such a tremendous variation in the amount of operative trauma, brain retraction, and hyperventilation. You could control adjuvant drugs carefully, but the operative site, where the retractors were placed, and other factors would introduce a lot of variance in the analysis.

DR. ROBINSON: Is there any advantage from use of desflurane with regard to indications to initiate steps such as computed tomography scan or reoperation at an earlier point in time, or is it too early to tell?

DR. YOUNG: Anyone who handles neurosurgical cases knows that you may have a situation where a patient does not emerge from anesthesia, and the question is always whether or not this is residual drug effect, or a problem that is surgical. More often than not, it is due to something that happened intraoperatively to the brain, unless you know that you have administered too much anesthetic. I think it is a question that is probably worth looking at in a systematic fashion.

DR. RAMPIL: I think the study you might want is to examine something like brain retraction pressure during these cases and how much retraction pressure was required to achieve a specific field-of-view. You would want to consider how much pressure is under the retractor and how much ischemia you might generate from that.

DR. ROBERT G. MERIN (Houston): Do you think that we still do not know quite enough to be able to label desflurane for use in neuroanesthesia?

DR. YOUNG: Let me put it in perspective. As far as I know, there has never been a case report of someone dying during induction from increased intracranial pressure secondary to any potent volatile anesthetic. In contrast, Giannotta et al. reported a 1% incidence of aneurysm rupture during anesthetic induction of patients undergoing craniotomy for aneurysm clipping (Giannotta SL, Oppenheimer JH, Levy ML, Zelman V. Management of intraoperative rupture of aneurysm without hypotension. Neurosurgery 1991;28:531–6). Batjer and Samson have reported similar data (Batjer H, Samson D. Intraoperative aneurysmal rupture: incidence, outcome, and suggestions for surgical management. Neurosurgery 1986;18:701–7). This might be related to several things, but most people would think that major increases in arterial pressure during induction would play a role. With respect to the cerebral effects of desflurane, I do not think there is compelling evidence that indicates it to be unsafe for neurosurgical patients. I would caution clinicians who elect to use desflurane in a patient who has a recently ruptured cerebral aneurysm to be sure to monitor arterial pressure closely.

An Overview of Induction and Emergence Characteristics of Desflurane in Pediatric, Adult, and Geriatric Patients

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A major advantage of desflurane over currently available agents is that the blood-gas partition coefficient of desflurane is 0.42, lower than all available volatile anesthetics, and slightly lower than nitrous oxide. This property predicts rapid induction of and recovery from general anesthesia with desflurane. This review will summarize and compare results of studies that have examined various clinical characteristics of induction and emergence with desflurane in a variety of patient populations. Studies in pediatric patients, and in adults, have confirmed that inhalation induction with desflurane is rapid. However, there has been a high incidence of airway irritation and/or reactivity, including breath holding, coughing, excessive secretions, and laryngospasm. This incidence is significantly higher than that seen with halothane, making it unlikely that desflurane will supplant halothane for inhalation inductions. The hemodynamic effects of desflurane induction and maintenance with or without intravenous adjuvants appear similar to those seen with isoflurane. Several studies have compared emergence from anesthesia with desflurane with that from isoflurane-based anesthetics, and have demonstrated that initial emergence from a given depth of anesthesia, e.g., time to eye opening or response to verbal commands, is about twice as fast with desflurane. Similar results have been obtained in pediatric patients where emergence from desflurane is faster than that seen from halothane. Emergence from desflurane anesthesia appears similar in time-course to that from propofol-based anesthetics. Psychometric testing has also confirmed more rapid emergence with desflurane than isoflurane, and the clinical impression has been that patients are more "awake" in the postanesthesia care unit, although studies have not demonstrated earlier discharge times from the postanesthesia care unit or from the hospital for ambulatory patients. Initial studies in elderly (>age 65 yr) patients have confirmed the safety of desflurane and generally confirmed the emergence and hemodynamic profiles demonstrated in younger age groups. Desflurane appears to offer some advantages over currently available anesthetics; the specific indications and potential for desflurane should become clearer over the next (first) few years of clinical use.

(Anesth Analg 1992;75:S38–46)

An ideal anesthetic should allow rapid, pleasant, and predictable induction of anesthesia, stable maintenance, and rapid, smooth emergence from the anesthetic state. Desflurane is a new polyfluorinated volatile anesthetic that has been undergoing clinical evaluation. Desflurane is synthesized from isoflurane by replacement of the chlorine atom in isoflurane by fluorine. This single change results in a molecule with a lower boiling point and considerably lower blood solubility than other available volatile anesthetics (Table 1). The low blood-gas (0.42) and brain-blood (1.3) partition coefficients of desflurane (vs 1.4 [1] and 1.6 [2] for isoflurane) predict that induction of and emergence from desflurane anesthesia should be significantly more rapid than that from isoflurane or halothane. Over the past several years, a number of clinical studies have been performed to examine whether the low partition coefficients and rapid uptake and elimination of desflurane in animals and in human volunteers are translated into rapid induction and emergence in patients undergoing surgery. This article will summarize the findings of these studies performed in a variety of surgical patients and will discuss the currently available information with regard to induction and emergence characteristics of desflurane in pediatric and adult patients, with some preliminary data on use and effects of desflurane in the elderly.

Induction

Volatile agents are used during induction either as the primary anesthetic agent, with or without nitrous

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Table 1. Physical Properties of Volatile General Anesthetics[a]

	Des	Iso	Halo	Enf	Sevo
Molecular wt (Da)	168	184.5	197.4	184.5	200
Boiling point (°C)	23.5	48.5	50.2	56.5	58.5
Vapor pressure (mm Hg at 20°C)	664	239	244	172	160
Partition coefficient					
Blood-gas	0.4	1.4	2.3	1.9	0.6
Olive oil-gas	19.0	91.0	224.0	96.0	53.0
MAC (%)	6.0	1.2	0.7	1.6	2.0

Des, desflurane; Iso, isoflurane; Halo, halothane; Enf, enflurane; Sevo, sevoflurane; Da, daltons; MAC, minimum alveolar concentration.
[a]Adapted from Jones (1).

oxide (N_2O) (inhalation induction), or are administered after induction of anesthesia/amnesia with intravenous agents to deepen anesthesia, decrease airway and cardiovascular responses, and start the maintenance phase of the anesthetic. Relevant concerns about inhalation induction include the subjective nature of the experience for the patient, airway irritation and excitement, hemodynamic and respiratory characteristics, and speed of induction. When potent inhaled agents are used to supplement intravenous induction, the subjective variables (e.g., pleasant vs unpleasant smell) are removed, and speed of uptake of the agent is somewhat less critical, but issues of cardiovascular, airway, and respiratory responses are still operative. The physicochemical properties of desflurane (3) and initial reports in volunteers (4) suggested that desflurane might be useful for inhalation induction or after intravenous induction, and a number of investigations were undertaken to evaluate the effects of desflurane administration during induction of anesthesia.

Pediatric Patients

Many pediatric anesthetics are commenced via inhalation. Halothane is usually chosen over isoflurane because it is more pleasant to breathe and less irritating to the airway (5). The first report of human administration of desflurane was in adult male volunteers, who were given desflurane at inspired concentrations of 1.8% or 5.4% (~0.25 or 0.75 MAC). Jones et al. (4) reported that these subjects found the agent "not unpleasant to breathe" and that it appeared to lack irritant respiratory effects. The authors suggested that desflurane might be useful for inhalation induction in pediatric anesthesia (4). Initial reports in children indicated that rapid induction by inhalation of desflurane was possible, with loss of consciousness in 1–2 min (6,7). A fairly high incidence of airway problems were reported, including breath holding, coughing, and excessive secretions, similar to that seen with isoflurane. Taylor and Lerman (8) have recently reported on induction of anesthesia with desflurane in 66 pediatric patients aged 1 mo to 12 yr. Patients breathed desflurane in 95% oxygen, with the desflurane concentration increased rather rapidly, by 7% increments every three to four breaths, to final inspired concentrations of 20%–25% (MAC of desflurane in infants and children is ~8%–10% [9]). Eyelash reflexes were lost at 1–2 min, and intubation could be performed at 4–5 min. Cardiovascular effects were acceptable with 20%–30% decreases in blood pressure before incision, and muscle relaxation was excellent. Unfortunately, the incidence of airway problems was unacceptably high. All patients experienced a period of "excitement." Fifty percent (33 of 66) experienced breath holding, 36% had more than two instances of coughing, and laryngospasm occurred in 30% (20 of 66). Two of the latter patients required succinylcholine, although it was noted that these two patients were treated early in the authors' experience with desflurane and had suffered recent upper respiratory tract infections. Airway complications contributed to decreased arterial oxygen saturation during induction to <90% in 18% of patients. Increasing inspired desflurane concentrations more slowly during induction appeared to worsen the incidence of airway complications. In this study, there was no control group receiving halothane or isoflurane with which to compare these results. A similar high incidence of airway problems with desflurane inhalation induction has been confirmed in a multicenter U.S. trial, in which the control group received halothane for induction and had airway complication rates of only 1%–4% (J. Lerman, personal communication). It should be noted that in the Taylor and Lerman study (8), desflurane was administered without premedication or N_2O. It was considered possible that the addition of premedication or N_2O, or both, might ameliorate some of these irritant/excitatory phenomena. Despite the above, data from other centers do not support any significant amelioration by these adjuncts on airway reactivity. It appears unlikely that desflurane will supplant halothane as the agent of choice for inhalation induction in children (6).

Adults

Several investigators have reported on inhalation induction with desflurane in adults (10–12), with results similar to those seen in the pediatric population (Table 2). Loss of consciousness occurs within 1–3 min, but the incidence of airway problems is significant and is not greatly affected by concurrent use of N_2O or fentanyl (11,12). Use of N_2O during

Table 2. Airway Complications During Desflurane Induction in Adults

	Rampil et al. (10) (n = 44)	Wrigley et al. (11) (n = 30)	Van Hemelrijck et al. (12) (n = 46)
Apnea (%)	0	NR	22
Breath holding (%)	NR	27	33
Laryngospasm (%)	4	NR	4
Coughing (%)	48	54	26
Secretions (%)	38	NR	7
Failure (%)[a]	18	10	2

NR, not reported.

[a] Abandoned inhalation route or administered muscle relaxant when not planned.

inhalation induction does appear to speed induction; loss of eyelash reflex was reported in an average of 124 s with desflurane in O_2 and 100 s with desflurane in 60% N_2O in one study (12); and at 2.0 min with N_2O and 2.6 min with desflurane in O_2 in another (11).

The pharmacokinetics of desflurane have suggested to some that a "single-breath induction" technique might be possible. Preliminary reports have suggested rapid induction and a relatively low incidence of airway problems by administering 2 MAC desflurane after a vital capacity exhalation, particularly in premedicated patients (13,14). This is an intriguing and interesting observation, but it appears unlikely that either conventional or single-breath desflurane inhalation induction in adults has much of a future.

The most common use of desflurane during the induction period will likely be after intravenous induction, to deepen and maintain anesthesia. In our own work comparing desflurane with isoflurane, both agents were administered after induction with thiopental (15). Under these conditions, we observed an incidence of airway reactivity with desflurane that was similar to or perhaps slightly greater than with isoflurane. Increasing the inspired concentrations of desflurane more rapidly did seem to decrease these problems, as reported (8). We compared the hemodynamic effects of desflurane versus isoflurane administration after intravenous induction with thiopental. Over the first 5 min, both isoflurane and desflurane were associated with significant increases in blood pressure and heart rate over preinduction values, greater with desflurane than isoflurane (unpublished observations). This tachycardia and relative hypertension may be related to an excitement phase of anesthesia (11), and the hemodynamic or clinical significance is unclear. Future studies will need to investigate and clarify the hemodynamic effects of desflurane in common clinical settings. Premedication and anesthetic adjuvants, especially opioids, may dramatically alter many of these hemodynamic effects. In at least one report in which an induction technique similar to ours was used, no difference in the hemodynamic effects of isoflurane and desflurane was detected after thiopental induction (16).

Geriatric Patients

Little information is available about desflurane use in elderly patients. A single preliminary report has claimed little problem with airway irritation/excitement in elderly (>65 yr) patients who had anesthesia induced with small doses of fentanyl (≤ 2 μg/kg) and thiopental (70–100 mg), followed by mask ventilation with desflurane (K. Zahl, personal communication).

The future usefulness of desflurane as an induction agent appears to be limited. Despite kinetics that theoretically indicate rapid induction and excellent muscle relaxation, its pungent odor and airway irritant/excitatory effects make it inferior to halothane for inhalation induction. Some of these problems may be minimized with appropriate premedication, coadministration of N_2O, or increasing the inspired concentration of desflurane very rapidly, but none of these maneuvers are likely to make desflurane popular as an induction agent.

Maintenance

It is clear that desflurane provides a stable anesthetic state during a variety of surgical procedures (8,12,15, 17,18). The cardiovascular effects of desflurane are similar to its close relative isoflurane. Similarly, the direct muscle relaxant effects of desflurane and its potentiation of nondepolarizing muscle relaxants, are also similar to or slightly greater than isoflurane (19–21). The solubility/kinetic characteristics of desflurane suggest advantages over currently available agents during surgery, allowing more rapid alterations in anesthetic depth than are possible with currently available agents. This may allow better control during changing surgical events that require deepening or lightening of the anesthetic state. At present, details of the actual potential and use of desflurane during the operative procedure have received limited attention. Reversal of the anesthetic state is the particular alteration of anesthetic depth that has received the most attention, because it is easiest to assess.

Emergence

Pediatric Patients

Taylor and Lerman (8) reported on recovery characteristics of desflurane in children. End-tidal desflurane concentrations decreased approximately 85% in the first 2 min after the agent was discontinued, and emergence as judged by eye opening was rapid, 6.1 ± 2.2 min. There was no control group that received isoflurane or halothane, but the authors cite published studies to suggest that this is less than the expected emergence time from isoflurane or halothane anesthetics of this duration (5,22,23). In a preliminary report of a controlled study comparing desflurane with halothane, maintenance anesthesia with desflurane did result in more rapid awakening (6). Three groups were compared: halothane induction with halothane maintenance; halothane induction with desflurane maintenance; and desflurane induction with desflurane maintenance (all with N_2O). The two groups receiving desflurane for maintenance each awoke in the operating room an average of 3.7 min after the anesthetic was discontinued, compared with 8.6 min in the halothane-halothane group. Given the problems (vide supra) with inhalation induction with desflurane and the possible advantages of desflurane as a maintenance agent allowing rapid emergence, this halothane-desflurane strategy may become popular to use in pediatric patients. Initial reports from the multicenter trial of desflurane in the United States appear to confirm that the rapid emergence from desflurane anesthesia is retained when anesthesia is initially induced with halothane (J. Lerman, personal communication). None of the investigators have noted airway problems or excitement during emergence from desflurane anesthesia in the pediatric population (8; J. Lerman, personal communication).

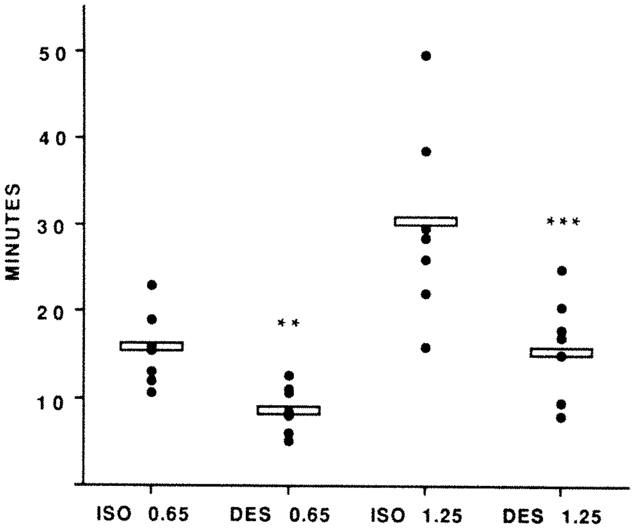

Figure 1. Individual emergence times for 28 subjects receiving desflurane (DES) or isoflurane (ISO) at 0.65 or 1.25 MAC with 60% nitrous oxide. *Rectangles*, means for each group. $^{**}P < 0.01$ versus ISO 0.65%. $^{***}P < 0.05$ versus ISO 1.25%. (Original figure from Smiley et al. [15]. Reproduced with permission of author and publisher.)

Adults

Comparison with isoflurane. We performed a controlled, randomized, prospective study to compare speed of emergence from desflurane versus isoflurane anesthesia in 28 adult patients aged 18–65 yr undergoing elective surgery (15). They were assigned to one of four groups ($n = 7$ per group) to receive isoflurane or desflurane at 0.65 or 1.25 MAC, along with 60% N_2O for maintenance of anesthesia. All patients were premedicated 5 min before induction with 0.03 mg/kg of midazolam, and anesthesia was induced with 5 mg/kg of thiopental (a few patients received additional 1–2 mg/kg of thiopental to treat excitement during induction), followed by isoflurane or desflurane in 60% N_2O-O_2 by mask to facilitate intubation without muscle relaxation. After intubation, the anesthetic concentration was adjusted to the appropriate end-tidal concentration using MAC values of 1.28% for isoflurane and 7.25% for desflurane. Subsequent to the study design, more detailed studies of desflurane MAC have revealed a 7.25% MAC value for young (18–30 yr) patients, whereas desflurane MAC in 30–65-yr-old patients has been reported to be 6.0% (10). The ages of all groups in our study were similar, so that this should have had little effect on the overall results. No opioids were administered until after emergence from anesthesia. End-tidal anesthetic concentrations were kept stable until near the end of surgery (average anesthetic exposure time was 113 min); then all anesthetic gases were discontinued. Ventilation with 100% O_2 was continued to maintain end-tidal Pco_2 at 35–40 mm Hg. The time until the patient opened his or her eyes and squeezed the investigator's hand in response to command was recorded (defined as "emergence time"). At each MAC concentration, emergence time was significantly less in the desflurane groups. At 0.65 MAC, emergence time was 15.6 ± 4.3 min (mean ± SD) for isoflurane and 8.8 ± 2.7 min for desflurane. At 1.25 MAC, the times were 30.0 ± 11.0 and 16.1 ± 6.0 min for isoflurane and desflurane, respectively. The individual patient data are illustrated in Figure 1. Of note, although we did see evidence of significant airway irritation (laryngospasm, coughing) during induction, we did not see any signs of this during emergence.

A similar study that also included preoperative and postoperative neuropsychologic testing ("psychometrics") was reported by Ghouri et al. (18). Thirty-eight outpatients undergoing relatively minor surgery (laparoscopy arthroscopy, superficial surgery) were studied. Preoperatively, psychometric testing consisted of a Trieger test (a "connect-the-dots" test of psychomotor function), visual analogue scales to assess subjective symptoms (e.g., pain, drowsiness), and the digit-symbol substitution test, in which numbers and symbols need to be matched in a given time period to assess cognitive capability.

Table 3. Emergence Time (Eye Opening) From Isoflurane-Nitrous Oxide and Desflurane-Nitrous Oxide Anesthesia

	Desflurane	Isoflurane
0.5 MAC[a]	5 ± 2	10 ± 8
0.65 MAC[b]	9 ± 3	16 ± 4
1.25 MAC[b]	16 ± 6	30 ± 11

MAC, minimum alveolar concentration.
Data are minutes ± SD.
[a] Data from Ghouri et al. (18); $n = 21$ for isoflurane, 17 for desflurane.
[b] Data from Smiley et al. (15); $n = 7$ per group.

Patients received fentanyl (3 μg/kg) and thiopental (4 mg/kg) for induction, with intubation facilitated by succinylcholine. Anesthesia was maintained with 3.0% desflurane ($n = 21$) or 0.6% isoflurane ($n = 17$) and 60% N_2O (~0.5 MAC volatile agent assuming 6% MAC for desflurane). The agent was discontinued at beginning of skin closure, N_2O was discontinued after skin closure, and ventilation was continued to maintain end-tidal Pco_2 at 35 mm Hg. Average anesthetic exposure was approximately 2 h for each anesthetic. Eye opening and hand squeeze were assessed as in our study from the time of discontinuation of the volatile agent (15). At 30, 60, and 90 min after recovery room admission, psychometric tests were repeated and compared with preoperative values and between the anesthetics. Initial emergence times were similar to the results in our study, with desflurane patients opening their eyes in 5.1 ± 2.4 min and isoflurane patients responding in 10.2 ± 7.7 min. The desflurane end-tidal concentration decreased 50% in 2.5 min, compared with 9.5 min for isoflurane. This is consistent with previous data in volunteers (24,25). In both studies, patients emerged approximately twice as fast from desflurane anesthesia as from isoflurane at each MAC concentration. The data from both studies are combined in Table 3, which reveals the expected trend toward longer emergence times with higher concentrations of anesthetics and the consistent results between the two studies. In addition to average emergence times twice as long with isoflurane, the standard deviations are correspondingly greater. Some patients do have significantly prolonged emergence from isoflurane. This could be less troublesome with desflurane.

The results of the psychometric testing also demonstrated more rapid emergence from desflurane than from isoflurane. At 30 min postoperatively, only 9 of the 21 isoflurane-group patients could perform the tests, whereas 13 of 17 desflurane-group patients could. By 60 min, the participation rates were no longer significantly different, but throughout the postoperative period, desflurane patients performed consistently better on both the subjective analogue scales and the digit-symbol substitution test, even with the higher participation rate in the desflurane group. There was no difference in performance on the Trieger (psychomotor) test, although as mentioned, fewer isoflurane-group patients were able to perform the test at 30 min. Desflurane patients rated themselves more comfortable by a linear analogue score than did isoflurane patients at all time points measured. It is possible that low residual postoperative concentrations of isoflurane are somehow "antianalgesic," or that residual sedation leads to confusion of other sensations as pain, or that the slight remaining concentrations of desflurane are analgesic. It may simply be that the more awake patients are better able to deal with pain and thus feel less subjective discomfort. There was no difference between the anesthetics in home discharge. It is unclear whether this is because there was no significant difference in recovery of psychomotor function, as suggested by similar Trieger test results, or was a result of the research protocol itself with prolonged postoperative testing or standard protocols of the particular outpatient surgery service, or both. Fletcher et al. (17) have reported findings quite similar to those of Ghouri et al. (18) and our own study, although the difference in initial emergence time between isoflurane and desflurane was 35% rather than 50%.

A preliminary report from a multicenter study further supports the previous findings (K. Zahl, personal communication). Laparoscopy patients in whom anesthesia was induced with fentanyl (1–2 μg/kg) and thiamylal until loss of eyelash reflex were randomized to receive desflurane or isoflurane at 1 MAC concentration, with or without 60% N_2O. Initial recovery was approximately 20% faster in the desflurane groups than the corresponding patients receiving isoflurane. Emergence (eye opening) after 1 MAC desflurane in O_2 occurred in 5.6 min, versus 8.5 min for isoflurane. Addition of 60% N_2O (keeping the volatile agent at 1 MAC concentration) increased these emergence times to 8.2 and 10.7 min, respectively. Other measures of initial emergence (patient's ability to state name, date of birth, etc.) followed the same pattern. Psychometric testing revealed results similar to Ghouri et al. (18), and discharge times again were not different between groups.

Comparison with propofol. For very minor, short procedures, especially outpatient procedures, the appropriate comparison for desflurane may be with propofol rather than isoflurane, because propofol has been associated with more rapid emergence than isoflurane (26). Two recent studies following similar protocols have reported comparisons between desflurane and propofol for outpatient surgery. Wrigley et al. (11) studied 60 outpatients assigned to four groups. Anesthesia was induced in group 1 with propofol (2.5 mg/kg), followed by maintenance with 6% desflurane (1 MAC) and 60% N_2O in O_2. Anesthesia was induced similarly in group 2 with propofol, followed by a maintenance infusion of propofol ($9\ mg\cdot kg^{-1}\cdot h^{-1}$ for 15 min followed by $6\ mg\cdot kg^{-1}\cdot h^{-1}$ thereafter). In group 3, anesthesia was induced by inhalation of desflurane in 60% N_2O and maintained with 6% desflurane in 60% N_2O, and group 4 received desflurane in O_2 for induction and maintenance with 6% desflurane in O_2. All groups received fentanyl ($\leq 2\ \mu g/kg$) during induction, and underwent tracheal intubation after loss of consciousness with the aid of muscle relaxants. At the end of surgery, the anesthetics were discontinued and time until emergence assessed. Patients receiving desflurane for induction and maintenance awakened numerically but not statistically significantly faster than those patients who received propofol. Patients opened their eyes to command in 6.2 min in group 4 (desflurane in O_2) compared with 9.4 min in group 2 (propofol induction and maintenance), and other measurements of awareness followed the same pattern. Psychomotor testing revealed numerical but not significantly slower recovery of preoperative function in those patients receiving propofol for induction and maintenance. There was similarly nonsignificant tendency toward an increased incidence of nausea and vomiting in patients who received desflurane. Only 1 patient in group 2, the propofol-propofol group, experienced nausea (7%), whereas a total of 16 patients in the other three groups experienced nausea (36%), with four episodes of vomiting, all in group 3, who received desflurane-N_2O for induction and maintenance. It is unclear whether these results are due to an antiemetic effect of propofol (27) or an emetic action of N_2O or desflurane, or both.

Van Hemelrijck et al. (12) reported on a study with a very similar protocol and the same four groups, except that the maintenance anesthetic was adjusted (50–$200\ \mu g\cdot kg^{-1}\cdot min^{-1}$ for propofol; 4%–7% for desflurane) according to patient responses (12). There was a trend toward more rapid initial awakening among those patients who received desflurane for maintenance compared with those who received propofol, achieving statistical significance in the desflurane in O_2 induction and maintenance group in 4.5 min versus 7.3 min in the propofol induction-propofol maintenance group. It is interesting that in this study where anesthetic depth was controlled according to patient response, patients receiving desflurane in O_2 awoke more rapidly than those receiving N_2O with desflurane. Psychometric testing did not detect significant differences between groups. There were no differences in time to sitting, standing, or discharge.

In summary, it appears that speed of emergence with desflurane is comparable to that from propofol-N_2O anesthesia. A preliminary report suggests that the same is true when comparing desflurane to alfentanil in outpatients (28). There is a higher incidence of nausea with desflurane, particularly in the presence of N_2O. A possible advantage of desflurane may be that its use could obviate the need for N_2O.

Geriatric Patients

Little has been published with regard to emergence from desflurane anesthesia in elderly patients. In general, older patients are more sensitive to sedatives, including general anesthetics, and take longer to awaken. Theoretically, desflurane might make emergence more predictable in the geriatric population. A report from the multicenter study comparing desflurane with isoflurane in elderly patients suggests results similar but less impressive than those seen in younger adults (R. L. Carpenter, personal communication). Anesthesia was induced with intravenous agents (fentanyl and thiopental), then maintained with isoflurane or desflurane, titrated to effect. Initial recovery times were 20% faster with desflurane, but the differences did not achieve statistical significance, and the times to recovery room discharge were not different. No psychometric or psychomotor testing was done, although the (nonblinded) observers suggested that desflurane patients appeared to be more "awake" at similar times after anesthesia. Incidences of complications (nausea, vomiting, intraoperative hemodynamic instability) were not different between anesthetics.

Summary

As predicted from its physicochemical properties, kinetics of induction and emergence (clinical correlates of uptake and elimination), appear to be more rapid with desflurane than with other volatile anesthetics. Owing to its somewhat unpleasant odor and propensity for causing airway reactivity, desflurane is unlikely to replace halothane as drug of choice for inhalation induction. The rapid uptake of desflurane may allow use of smaller doses of intravenous induction agents, because an anesthetic level of desflurane is likely to be more quickly attained. Decreased use of intravenous agents could lead to more rapid emergence, particularly from shorter-duration anesthetics. During maintenance, use of desflurane should allow more rapid alteration of level of anesthesia, which could prove useful for induction of deliberate hypotension or for treatment of major surgical events of short duration, without prolongation of the anesthetic. Initial emergence and postoperative recovery of mental function from desflurane anesthesia are rapid compared with isoflurane and similar to that from propofol-based anesthetics. These studies have not noted decreases in the average time spent in the recovery room or hospital. Given the variability among patients in emergence responses, it is possible that as larger numbers of patients receive desflurane they will experience fewer delayed awakenings requiring hospital admission after outpatient surgery than those patients who receive isoflurane. It will be important to investigate whether the more rapid emergence with desflurane results in fewer early airway and other complications during early recovery. Finally, it must be noted that most of the studies thus far have not been performed under normal clinical conditions; patients have been preselected, types of surgery controlled, and administration of the anesthetics has been under more or less strict guidelines. The true advantages or disadvantages of desflurane relative to current anesthetics will become more apparent after it is used in the normal clinical environment.

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DISCUSSION

DR. RYAN COOK (Pittsburgh): One conclusion from your pediatric multicenter study was that incidence of laryngospasm was comparable to that with isoflurane. I submit that there were no objective data presented to document that. The incidence is nowhere near 30% or more. Also, in looking at the ideal inhaled anesthetic agent, I would envision that there are many patients who might be induced for very short surgical procedures. Despite this, it seemed as though every patient in this cohort was tracheally intubated, mostly with succinylcholine. Therefore, what is the experience, if any, of unintubated patients being given desflurane-nitrous oxide by mask, a technique used on probably one-third of my clinical practice?

DR. RICHARD M. SMILEY (New York): In my experience, none. All of our patients were adults undergoing surgery of at least 1 h duration, and they were all tracheally intubated. I do not have any information on the pediatric population.

DR. RONALD D. MILLER (San Francisco): Were such studies performed?

DR. SMILEY: Not that I have seen, no.

DR. JERROLD LERMAN (New York): What data do we have with regard to spontaneous ventilation of the tracheally intubated or unintubated pediatric, adult, or geriatric patient, depending on your age of interest? The answer was that there have been no studies defined to address those issues. In view of the impression that at >1.5 MAC, the P_{CO_2} in some adults who are healthy may approach 88 with desflurane, and considering the role for desflurane as primarily a maintenance and recovery agent, I think these two areas must be addressed in future studies.

DR. CHARLES COTÉ (Boston): We talk about single-breath induction with halothane for children. When we do that, we normally fill the circuit with 5% halothane and 60% nitrous oxide, so that is approximately 7 MAC. You cannot do that with desflurane. Perhaps that is an issue that needs to be considered. As we observed when we attempted to do mask inductions in children, the incidence of laryngospasm was very high; and it was not just laryngospasm like that with halothane, it was a "near-death" experience, as our pediatric surgeons attested.

DR. SMILEY: In Dr. Lerman's data from Canada in 66 patients, I think he reported that 18% of the patients who were induced with desflurane had arterial oxygen saturations decrease below 90% during the induction, and this is with 95% oxygen. This was not single-breath induction.

DR. COTÉ: That is the difference. In the multicenter study, ours was not either; but in the multicenter study, nitrous oxide was part of the induction technique required by the protocol, and that, I think, was one of the problems with the protocol. If we had done the study as Dr. Lerman did with 100% oxygen, we would not have had the "near-death" experiences. So I think, despite protocol difficulties, these studies point the way to appropriate labeling. The last comment I wanted to make was about the emergence. We found that emergence was so rapid with desflurane that the children were greatly confused and disoriented in the recovery room.

DR. SMILEY: Well, I think there may be some difference between pediatric outpatients and adults (either outpatients or inpatients). I was concerned about allowing people to wake up so quickly with presumably so little residual anesthesia, but very few remembered pain. They may have been amnestic, perhaps, the first few minutes.

DR. DENNIS FISHER (San Francisco): When you talked about the pediatric studies, although you gave Dr. Lerman credit, several others who were involved in the U.S. multicenter trials also deserve to be mentioned: Drs. Maurice Zwass and Dennis Fisher from UCSF; Drs. Leila Welborn and Raafat Hannallah from D.C. Children's; Drs. Charle Coté and Lydia Liu from Massachusetts General; Drs. Pete Davis and Ryan Cook from Pittsburgh Children's.

DR. SMILEY: You are absolutely right. They all wer involved and should be acknowledged.

DR. FISHER: One of the points we have been interested i is that although it is easy to make a smooth transition fron a halothane induction, followed by intubation, to a desflurane anesthetic, we really do not know what will happen i you induce anesthesia with thiopental or propofol in children and then administer desflurane. Will we see th profound laryngospasm we have seen with desfluran inductions?

DR. SMILEY: In our 52 patients, we had 28 who receive desflurane. We had two incidences of laryngospasm i adults who had been induced with thiopental. In defense o desflurane, or in defense of our studies, they were two o our first four or five patients, so it was early in ou experience. Later, in our intravenously induced patients we got better at dealing with desflurane. We still had som coughing, a little breath holding, but we had no episodes laryngospasm requiring a muscle relaxant after our first fe patients.

DR. IRA RAMPIL (San Francisco): I would like to add m perspective, having done one of these induction, maintenance, and emergence studies, with regard to hypertensio and tachycardia seen during induction. We saw fairl uniform hypertension and tachycardia, but you should tak our data with a grain of salt, as is true for many othe studies done as phase I trials. Our protocol required us t be pharmacologically pure, to assess what desfluran would do by itself, so we did not premedicate the patients I think if you were to use desflurane the way you do a inhaled induction in adults with isoflurane, the incidenc and magnitude of this excitement phenomenon would b much muted. The few times I have administered isofluran without any other drugs, I have seen similar problems With regard to laryngospasm, in the approximately 6 patients I anesthetized with desflurane, we had only tw cases of laryngospasm, both of which may have bee matters of operator technique. I would also like to mentio our patients' experience with pain after the procedures. W found after our first few anesthetics that pain returned a quickly as consciousness, and in our patients, the latte returned quite rapidly. We found we needed to add morphine at the end of the cases.

DR. SMILEY: In the first 28 patients in our group of 50, w first allowed them to awaken. Then almost all were given or 10 mg of morphine or 100 μg of fentanyl or something o that sort. After just a few minutes had passed, they ha some opiate effect.

DR. R. D. MILLER: There is difficulty in determining level of patients' pain. Blinded studies are best to solicit whethe pain is there or not. In the future, that is such a soft are that we need to be precise as to how we make determinations that somebody has had pain.

DR. SMILEY: A weakness in studies like these is the fact they were not blinded because of the nature of the anesthesia machine used to administer desflurane. We always knew what the patient was receiving. The patients did not know, generally. They all assumed they were receiving desflurane.

DR. MIRIAM LEBENBOM-MANSOUR (Detroit): There were two things I wanted to comment about. One of them was that when we did our study in Michigan, we had two patients during induction who had significant hypertension, during which diastolic blood pressures were getting up to 110 mm Hg. We had to decide what we wanted to do, whether we wanted to turn off the desflurane and do something else with those patients. The hypertension was during induction in our studies. I do not recall whether Dr. Apfelbaum's cases were during induction or during maintenance.

DR. R. D. MILLER: Did you administer fentanyl ahead of time?

DR. LEBENBOM-MANSOUR: Yes, we administered fentanyl (2 μg/kg) up front. I do not know what that really means. We had 60 patients in our study and experienced this in only two. I also wanted to comment about emergence. Most studies appear to show differences only in terms of a few minutes, particularly if you compare propofol with desflurane. Do you really care whether emergence takes 3–5 min with either drug? If you look at discharge and recovery times in other ways, even comparing them with isoflurane, they certainly look very similar to me.

DR. SMILEY: Initial wake-up was significantly faster with desflurane, and in our studies not just a few minutes, but really half time, 15 min versus 8 min and 10 min versus 5 min. Recovery room discharge times were not different. One explanation could be simply that protocols in certain recovery rooms do not permit people to leave that soon. Another possibility is that there are insufficient differences an hour later to cause a difference in discharge time. Again, a subjective comment, but all of us who were working on it could tell (and the recovery nurses could tell) that this was a patient that got the "new drug." Patients seemed much happier with their anesthetic, felt better an hour or two later, some remarking "Gee, I am more 'with it', I do not have that weird feeling I had after my last one." Those are things I think are harder to prove. I am not sure how we get at that.

DR. R. D. MILLER: I tend to agree with you. To me, what is really important is, how do they feel 24 h later?

DR. RYAN D. COOK (Pittsburgh): I will be concise. I do not think the severity of the laryngospasm should be minimized, at least not from the pediatric studies. This was not straightforward laryngospasm easily reduced with positive pressure ventilation. This was severe, intractable, associated with severe hypoxemia in many cases, and required succinylcholine. In my experience, the laryngospasm was akin to that seen with cyclopropane in the old days. On the other hand, I also agree with the observation that perhaps there is a learning curve in the administration of desflurane. Despite that learning curve, it is my recollection that we saw as much laryngospasm late in the study as we saw early. In our institution, the wizened veteran who had administered all those terrible agents in antiquity had as much laryngospasm with desflurane as did the younger physicians.

DR. RANDALL L. CARPENTER (Seattle): Future studies should prompt, "When can patients stand? When can they void?" or whatever the criteria are for discharge. Our postanesthesia care unit nurses tend to have relatively fixed expectations of how long it should take for someone to recover from a given anesthetic. They are not comfortable sending, nor are they necessarily allowed to send, a patient out until a certain time lapses after a specific operation and anesthetic technique, unless you prompt for designated criteria. Otherwise, all patients are going to come out the same. Future studies should not assess discharge time unless you are prompting for proper endpoints.

DR. SMILEY: There are protocols and there are expectations in daily practice. I think you are absolutely right.

Studies of Desflurane in Outpatient Anesthesia

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The low solubility of desflurane contributes to rapid emergence after outpatient anesthesia. Compared with isoflurane, recovery times to eye opening, response to verbal commands, and orientation to person, place, and time have been significantly shorter. Even when compared with the rapid, short-acting intravenous anesthetic propofol for induction and maintenance of outpatient anesthesia, desflurane displayed more favorable early recovery characteristics. Although patients receiving desflurane are less sedated in the early postoperative period than those receiving propofol, times to ambulation and discharge were similar. The direct "antiemetic" activity of propofol may have contributed to a lower incidence of postoperative nausea and emesis versus desflurane. Finally, the effects of desflurane, isoflurane, and propofol on postoperative psychomotor (e.g., Trieger test, choice reaction time) and cognitive (e.g., digit-symbol substitution test, critical flicker fusion test) function are remarkably similar. Given its favorable early recovery profile, desflurane would appear to be a useful alternative to both isoflurane and propofol for maintenance of outpatient anesthesia. As desflurane is pungent and possesses respiratory irritant properties, propofol will likely remain the induction agent of choice in the outpatient setting. In conclusion, desflurane appears to have few adverse effects on recovery after ambulatory surgery, but nausea and emesis were lower with propofol. Desflurane's relative ease of administration versus propofol may be an important determinant of its future role in outpatient anesthesia.

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In considering possible roles for desflurane in outpatient anesthesia, it is important first to consider factors that contribute to successful anesthesia for ambulatory surgery. An optimal anesthetic for outpatient surgery would include the following:

1. These should have a rapid and smooth onset of action. Efficiency is an important factor in the ambulatory setting.
2. Intraoperative amnesia and analgesia are quite important, as is the ability to provide for excellent operating conditions.
3. There should be rapid recovery without residual side effects or clinically significant discomfort. Degree of postoperative pain is a major limiting factor in determining whether a surgical procedure can be performed on an ambulatory basis.
4. Absence of adverse effects, such as nausea and vomiting, is extremely important after ambulatory surgery; emetic symptoms affect not only recovery times but also the incidence of unanticipated hospital admissions.

Several years ago, Gold et al. (1) evaluated factors that contributed to unanticipated hospital admissions after ambulatory surgery. Of the factors associated with increased risk of unanticipated admissions, general anesthesia was at the top of the list. Despite the availability of more rapid and shorter acting anesthetics and analgesic and muscle relaxant drugs, general anesthesia is still associated with an enhanced risk of unanticipated hospital admission (compared with local or regional anesthesia) after ambulatory surgery.

A recent survey involving U.S. anesthesiologists indicated that the predominant drug for general anesthesia maintenance in the outpatient setting was isoflurane. Although many of the recent studies involving outpatients compared desflurane with propofol, that comparison may be less relevant because isoflurane is the drug that desflurane would be likely to replace.

Most investigations involving use of desflurane in outpatients have focused on its recovery profile. Ghouri et al. (2) evaluated a group of patients undergoing outpatient procedures lasting 1–3 h (e.g., plastic, gynecologic, and orthopedic procedures). Demographically, the isoflurane and desflurane groups were similar (Table 1). The total doses of fentanyl (3 μg/kg) and thiopental (4.2–4.4 mg/kg) were representative of dosages commonly used. Emergence was

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Table 1. Patient Demographic Characteristics and Adjunctive Drug Requirements in Two Study Groups[a]

	Isoflurane group (n = 21)	Desflurane group (n = 17)
Gender (M/F)	7/14	9/8
Age (yr)	40 ± 14	44 ± 11
Weight (kg)	74 ± 16	83 ± 16
Height (cm)	172 ± 9	169 ± 11
Duration of anesthesia (min)	127 ± 80	98 ± 55
Initial fentanyl dose (μg/kg)	3.1 ± 0.6	3.0 ± 0.5
Total thiopental dose (mg/kg)	4.4 ± 1.5	4.2 ± 0.9
Total fentanyl dose (μg/kg)	4.0 ± 1.4	3.5 ± 0.9
Total vecuronium dose (mg/kg)	0.07 ± 0.05	0.05 ± 0.03

Mean values ± SD.
[a] Data are from Ghouri et al. (2).

Table 2. Recovery Times After Discontinuation of Inhaled Anesthetic[a]

	Isoflurane group	Desflurane group
End-tidal agent concentration at end of surgery (%)	0.6 ± 0.2	2.9 ± 0.4[b]
Time to 50% decrease in end-tidal concentration (min)	9.5 ± 3.4	2.5 ± 0.8[b]
Time to opening eyes (min)	10.2 ± 7.7	5.1 ± 2.4[b]
Time to following commands (min)	11.1 ± 7.9	6.5 ± 2.3[b]
Time to sitting up in a chair (min)	113 ± 27	95 ± 56
Time to phase I to II transfer (min)	118 ± 36	105 ± 49
Time to "home-ready" (min)	231 ± 40	207 ± 54

Values are mean ± SD.
[a] Data from Ghouri et al. (2).
[b] Significantly different from isoflurane group; $P < 0.05$.

evaluated from equi-MAC concentrations (≈0.5 MAC). Steady-state end-tidal anesthetic gas concentrations at the end of the surgical procedures were 0.6% isoflurane and 2.9% desflurane. Both treatment groups also received the same concentration (70%) of nitrous oxide in oxygen. Compared with the isoflurane group, the time required for the end-tidal anesthetic concentration to decrease by 50% was significantly shorter in the desflurane group (Table 2). Times to emergence from anesthesia (i.e., eye opening and ability to follow commands) were also significantly shorter. There were no significant differences between the two anesthetic groups with respect to times to sitting up, to transfer from phase I to phase II recovery, and to being judged home-ready by postanesthesia care unit (PACU) staff using standardized discharge criteria. The study patients were required to complete a battery of postoperative tests, so potential differences in discharge times may have been obscured.

Intraoperative hemodynamic changes >20% above or below preinduction baseline values occurred with similar frequency in both treatment groups (Table 3).

Table 3. Adverse Intraoperative Cardiovascular Events and Side Effects in the Postanesthesia Care Unit[a]

Event	Isoflurane group	Desflurane group
Intraoperative[b]		
Tachycardia	3 (14)	0 (0)
Bradycardia	4 (19)	2 (12)
Hypertension	5 (26)	3 (18)
Hypotension	1 (5)	3 (18)
Postoperative (PACU)		
Nausea and vomiting	9 (43)	6 (35)
Pain	11 (52)	8 (47)

PACU, postanesthesia care unit.
Data presented as number (percent).
[a] Data from Ghouri et al. (2).
[b] Change in heart rate or blood pressure >20% of the preinduction baseline value.

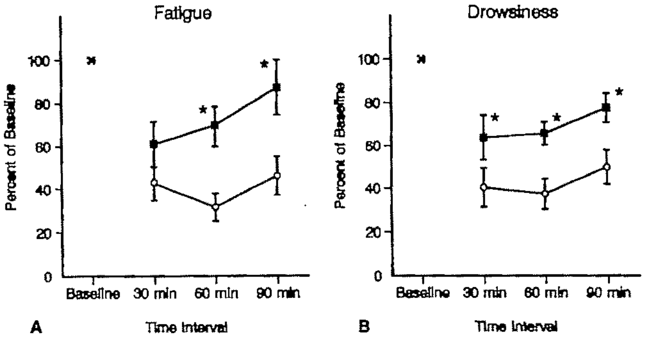

Figure 1. Visual analogue scales (-■-, desflurane; -○-, isoflurane). **A.** Fatigue; $^*P < 0.05$. **B.** Drowsiness; $^*P < 0.05$.

In the recovery room, nausea and vomiting occurred in 35% of outpatients receiving desflurane compared with 43% in the isoflurane group. Requirements for antiemetic therapy in the PACU were similar in both groups. Incidence of pain (i.e., patients who required parenteral analgesics in the PACU) was also nearly identical in the two groups.

Visual analogue scales were used to assess residual effects of the anesthetic agents to assess postoperative fatigue and drowsiness (Figure 1). At 30 min postanesthetic, there were significant decreases in both groups (compared with preoperative baseline values). There was less subjective impairment in the desflurane group compared with the isoflurane group at the 60- and 90-min time intervals. To evaluate psychomotor performance, the Trieger test was used. No differences were found between the two anesthetic groups in the early postoperative recovery period (Figure 2). Cognitive function was assessed with the digit-symbol substitution test (DSST). Postoperatively, only 43% of the isoflurane-treated patients could actually perform the test at the 30-min time point compared with 76% of the desflurane-treated patients. The desflurane group performed

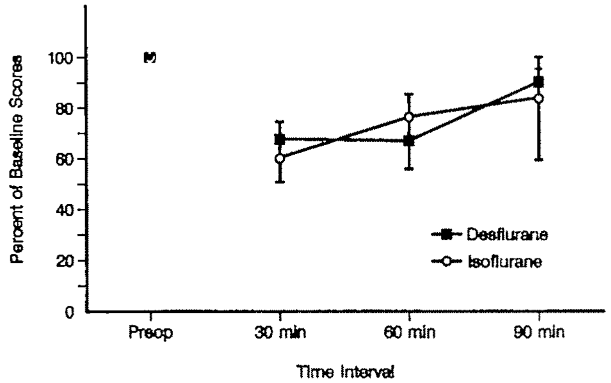

Figure 2. Trieger test.

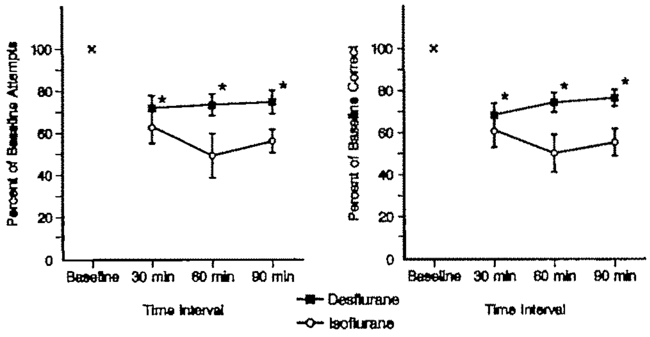

Figure 3. Digit-symbol substitution test. *$P < 0.05$.

significantly better overall on the DSST (Figure 3). Failure of test scores to return to preoperative baseline values in either group may have been related to the fact that patients in both groups were receiving parenteral analgesics for pain control and antiemetic drugs to control nausea and vomiting. These centrally active drugs can impair ability to perform cognitive function tests.

Others have evaluated inhaled agents on emergence times and psychomotor performance after outpatient procedures (3,4). Smiley et al. (3) reported shorter emergence times after desflurane versus isoflurane anesthesia. Fletcher et al. (4) evaluated early and late recovery of psychomotor performance after desflurane- and isoflurane-supplemented anesthesia. Outpatients were randomly assigned to one of four anesthetic treatment groups (Table 4). Three groups received thiopental for induction, followed by isoflurane-nitrous oxide (control), desflurane-nitrous oxide, or desflurane alone for maintenance of anesthesia. The final group received desflurane alone for induction and maintenance of anesthesia. These investigators found shorter emergence times when desflurane was used for maintenance of anesthesia compared with isoflurane (Figure 4). Use of thiopental (versus desflurane) for induction of anesthesia prolonged early recovery times after desflurane maintenance. Compared with isoflurane, the desflurane group had less residual impairment of choice reaction time (Figure 5). No differences were found between the two volatile anesthetic groups in performance on the critical flicker fusion threshold test (Figure 6). All four groups returned to baseline performance levels by 24 h.

More recent studies with desflurane have compared its recovery profile with that of propofol. Although some have suggested that propofol is an ideal anesthetic for outpatients, propofol possesses side effects, including (a) pain on injection; (b) cardiovascular depressant effects owing to direct effects on peripheral vasculature, baroreflex mechanisms, and direct myocardial depression; (c) respiratory depression as well as transient apnea and interference with central respiratory drive; and (d) excitement (euphoria) on emergence from anesthesia (5,6).

Outpatient studies comparing desflurane and propofol have been performed in the United States as well as the United Kingdom (7,8). In a group of outpatients undergoing laparoscopic procedures, desflurane was compared with propofol used for induction and maintenance of general anesthesia (7). These healthy young women were randomly assigned to one of four treatment groups (Table 5). Group I received propofol for induction, followed by propofol and nitrous oxide for maintenance. Group II received propofol for induction, followed by desflurane and nitrous oxide for maintenance. Group III received desflurane and nitrous oxide for induction and maintenance. Group IV received desflurane alone for induction and maintenance. Although the groups receiving desflurane with nitrous oxide (groups II and III) required lower end-tidal desflurane concentrations during maintenance than did the desflurane-alone group (Figure 7), emergence was significantly faster in the group receiving desflurane alone for induction and maintenance of anesthesia (Figure 8). Later recovery times (e.g., sitting up, standing, walking, discharge) were similar in all four groups (Figure 9).

In comparing the intraoperative hemodynamic changes, no significant differences were apparent between propofol and desflurane (with or without nitrous oxide) during maintenance (Figures 10 and 11). Side effects during the induction and early recovery period differed significantly among the various groups. Pain on injection was reported in 45% of the groups induced with propofol (Table 6). Respiratory irritation was more common with desflurane. Nitrous oxide did not alter the incidence of respiratory complications during induction with desflurane. Spontaneous movements during induction were noted in all four treatment groups.

Postoperatively, recovery of psychomotor function

Table 4. Demographic Characteristics of Patients in the Four Treatment Groups[a]

	Thio-Iso-N_2O group	Thio-Des-N_2O group	Thio-Des group	Desflurane group
Age (yr)	40.2 ± 2.72	39.4 ± 2.7	41.7 ± 3.0	41.7 ± 2.4
Weight (kg)	80.3 ± 2.8	78.1 ± 3.9	76.3 ± 2.7	73.3 ± 3.0
Height (cm)	169 ± 6.0	174 ± 3.2	169 ± 2.1	170 ± 11
Dose of thiopental (mg)	342 ± 15	369 ± 24	330 ± 14	—
Duration of anesthesia (min)	45.8 ± 5.1	50.4 ± 4.1	50.3 ± 6.3	53.6 ± 6.2
End-tidal anesthetic concentration at discontinuation (%)	1.1 ± 0.04	6.1 ± 0.34	8.9 ± 0.35	8.3 ± 0.41

Thio, thiopental; Iso, isoflurane; Des, desflurane.
Data are mean ± SE.
[a]Data from Fletcher et al. (4).

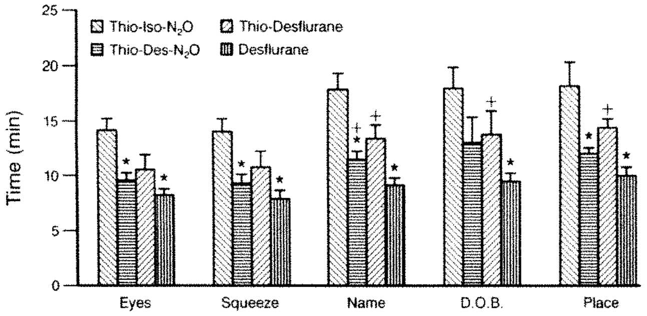

Figure 4. Early recovery times. Data are mean ± SE. $^*P < 0.05$ compared with Thio-Iso-N_2O group. $^†P < 0.05$ compared with Des alone group. D.O.B., date of birth.

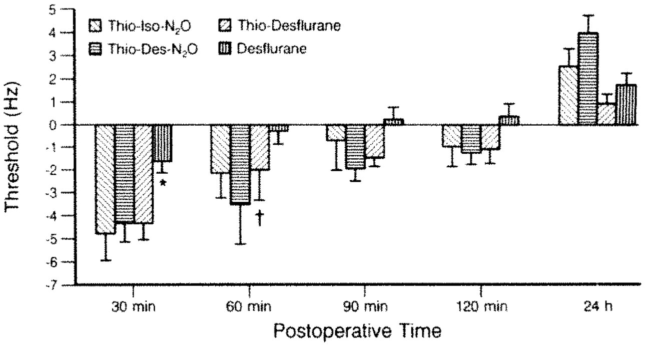

Figure 6. Critical flicker fusion thresholds. Data are mean ± SE. $^*P < 0.05$ compared with Thio-Iso-N_2O group. $^†P < 0.05$ compared with Des alone group.

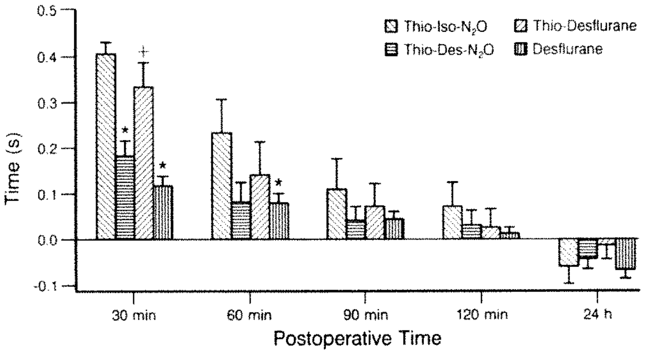

Figure 5. Choice reaction times. Data are mean ± SE. $^*P < 0.05$ compared with Thio-Iso-N_2O group. $^†P < 0.05$ compared with Des alone group.

was evaluated at 30-min intervals with the DSST. Although all four groups performed remarkably well (Figure 12), the group receiving propofol for induction followed by desflurane-nitrous oxide for maintenance (group II) recovered more slowly than those receiving propofol (group I) or desflurane (group IV) alone. Both the patients and a research nurse who was unaware of the experimental treatment evaluated residual levels of drowsiness in the PACU. At 30 min after surgery, patients who received desflurane alone tended to be more awake (and calm), compared with those assigned to group I receiving propofol alone or the propofol-desflurane-nitrous oxide group (group II) (Figure 13). Postoperative sedation scores were similar in all four groups and remained higher than the preoperative baseline values 2 h after the operation (Figure 14).

Using a similar protocol design, Wrigley et al. (8) reported that postoperative psychomotor performance (e.g., DSST, "p" deletion) in outpatients who had received propofol for induction and maintenance of anesthesia was "significantly worse compared with those who were given desflurane either for induction and maintenance or for maintenance only." Although these investigators also found a tendency for other recovery parameters to be faster in patients receiving desflurane (versus propofol), these differences were not statistically significant. Incidence of postoperative nausea and vomiting was not increased in the desflurane groups (versus propofol-nitrous oxide). In the previous study (7), a higher incidence of moderate to severe nausea was found in the desflurane treatment groups (52%–59% compared to 15% with propofol-nitrous oxide alone) (Figure 15).

Recently, Watcha et al. (9) reported that compared with a standard droperidol-halothane-nitrous oxide technique, propofol alone was associated with de-

Table 5. Demographic Characteristics of Patients in the Four Anesthetic Treatment Groups[a]

	Prop-N_2O group (n = 23)	Prop-Des-N_2O group (n = 23)	Des-N_2O group (n = 23)	Desflurane group (n = 23)
Group No.	I	II	III	IV
Age (yr)	31 ± 6	28 ± 6	30 ± 5	31 ± 6
ASA physical status (I/II)	20/3	19/4	21/2	18/5
Weight (kg)	63 ± 9	65 ± 17	71 ± 14	64 ± 9
Procedures (n)				
Diagnostic	6	6	8	6
Laser treatment	3	4	2	4
Tubal ligation	14	13	13	13
Operating time (min)	38 ± 28	50 ± 37	44 ± 29	36 ± 26
Anesthesia time (min)	56 ± 30	68 ± 38	61 ± 31	55 ± 29
PACU fentanyl (μg)	70.5 ± 91	51.5 ± 65	27.3 ± 38	37.3 ± 50

PACU, postanesthesia care unit; Prop, propofol; Des, desflurane.
Values are mean ± SD or numbers.
[a] Data from Van Hemelrijck et al. (7).

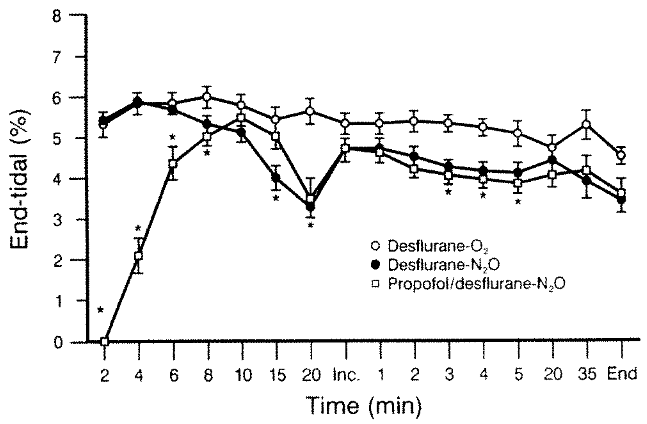

Figure 7. Desflurane concentrations. *$P < 0.05$ compared with group IV (Des alone).

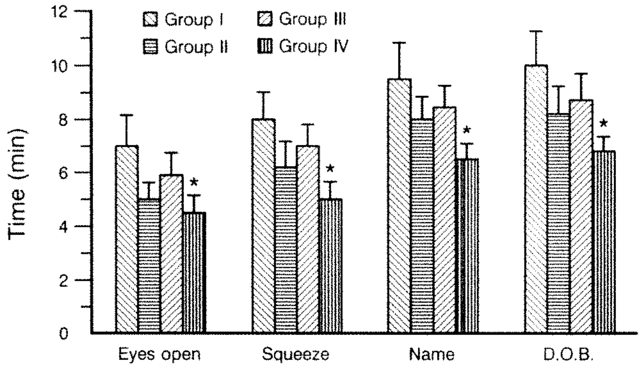

Figure 8. Emergence times. *$P < 0.05$, compared with group I (Prop alone). D.O.B., date of birth.

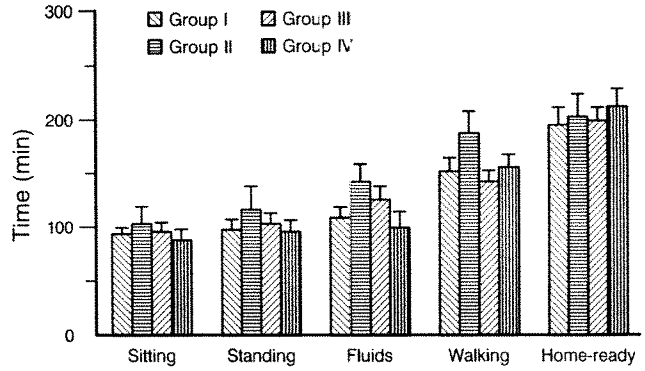

Figure 9. Recovery events.

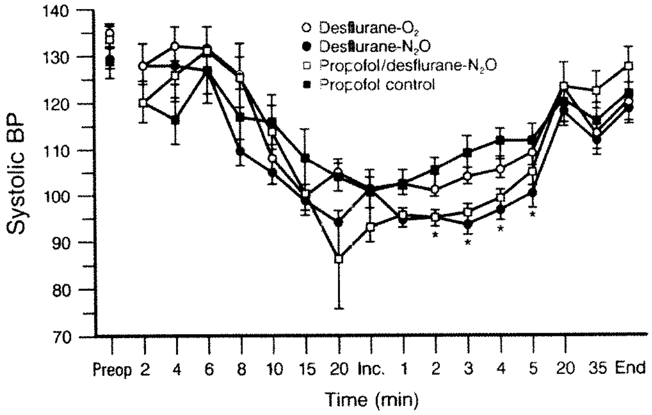

Figure 10. Intraoperative hemodynamic changes: systolic blood pressure (BP). *$P < 0.05$ compared with group I (Prop alone).

creased emesis after strabismus surgery in pediatric outpatients. These data suggested that propofol may possess antiemetic properties.

Postoperative nausea and vomiting is a problem that importantly affects recovery after outpatient surgery (1). In reviewing the anesthetic-related causes of unexpected hospitalizations after ambulatory surgery, intractable nausea and vomiting is usually at the top of the list for both adults and children (10). Even if not intractable, nausea or vomiting clearly impacts recovery after outpatient surgery (11). Times

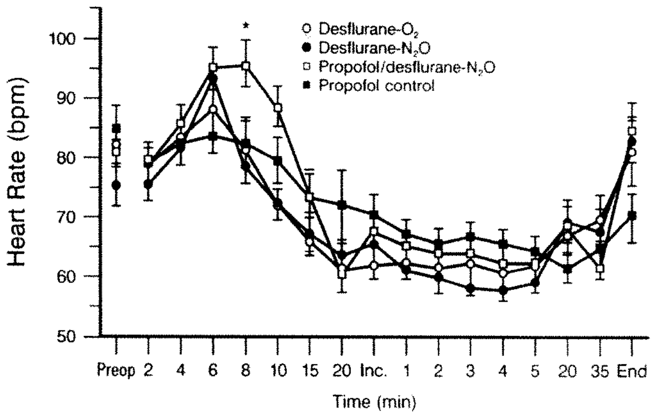

Figure 11. Intraoperative hemodynamic changes: heart rate. *$P <$ 0.05 compared with group III (Des-N_2O).

Table 6. Incidence of Complications Associated With Induction of Anesthesia[a]

Complication	Propofol	Desflurane +N_2O	Desflurane
Pain on injection	41 (19)	0[b]	0[b]
Apnea	2 (1)	17 (4)	26 (6)[b]
Breath holding	0	26 (6)[b]	39 (9)[b]
Laryngospasm	0	4 (1)	4 (1)
Coughing	4 (2)	30 (7)[b]	22 (5)[b]
Excess secretions	0	4 (1)	9 (2)
Spontaneous movements	21 (10)	30 (7)	48 (11)

Data presented as number (percent).
[a] Data from Van Hemelrijck et al. (7).
[b] Significantly different from control (group I); $P < 0.05$.

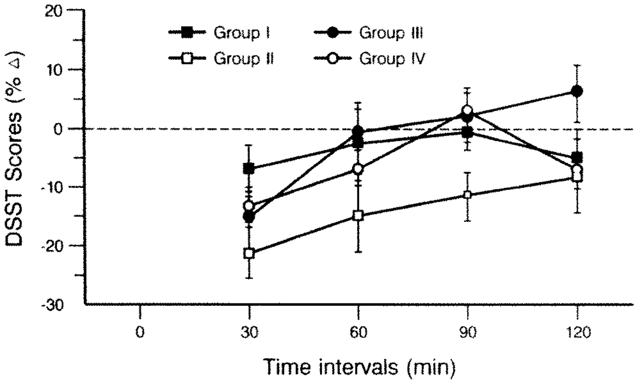

Figure 12. Recovery of cognitive function. DSST, digit-symbol substitution test.

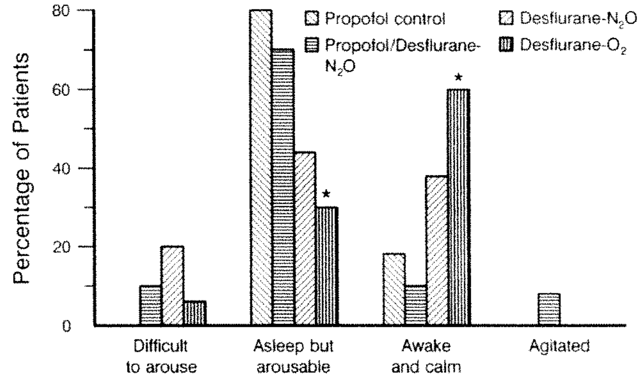

Figure 13. Postoperative sedation (at 30 min after surgery). *$P <$ 0.05 compared with control (group I).

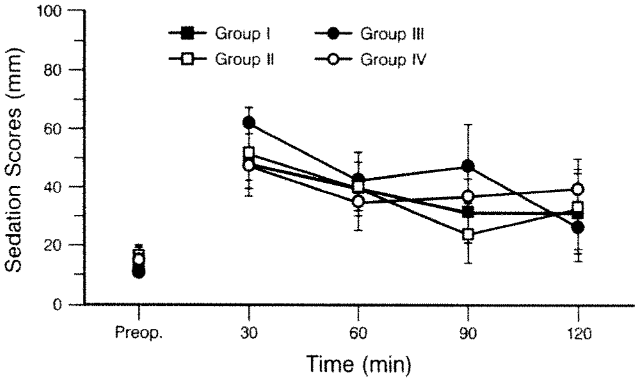

Figure 14. Recovery from sedative effects.

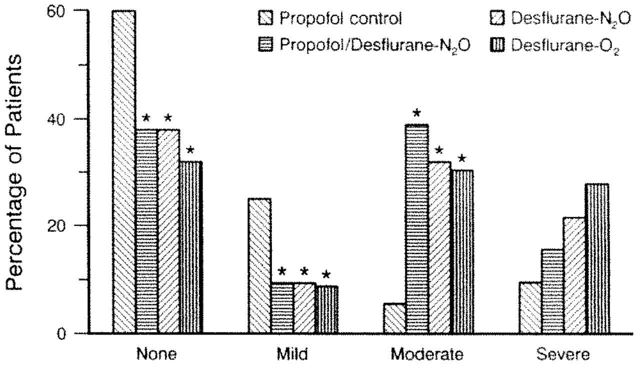

Figure 15. Postoperative nausea. *$P < 0.05$, compared with control (group I).

to ambulation and discharge were significantly prolonged with nausea alone and further prolonged when nausea was associated with vomiting. All studies involving desflurane (and propofol) have focused on emetic symptoms in the PACU. Actually, nausea and vomiting after discharge from an ambulatory surgery center may be more important from the patient's perspective. Most recent clinical reports describing the newer short-acting anesthetic, analgesic, and muscle relaxant drugs are lacking in good outcome data with regard to outpatients after discharge to their homes (i.e., when do patients resume their normal activities?).

Finally, an editorial appeared in the *Lancet* when propofol was released in Europe several years ago in which the writer suggested that the "new awakening in anesthesia [was coming] at a price" (12). Although not referring merely to the cost of propofol, the author made the astute observation that if patients awakened rapidly, they might be more aware of events in their surrounding environment, including postoperative pain. Pain control after ambulatory surgery will be increasingly important as we utilize shorter acting anesthetics and analgesics during outpatient anesthesia.

Availability of a less soluble volatile anesthetic (desflurane) will provide more rapid emergence from outpatient anesthesia than isoflurane. Cost-effectiveness and outcome studies are needed to determine the future role of desflurane in ambulatory surgery (13,14).

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DISCUSSION

DR. RONALD D. MILLER (San Francisco): The presence of nausea and vomiting may well be more important than several other anesthetic-related factors in determining when people go home from ambulatory surgery. If that is the case, why use fentanyl so often at the start of anesthesia?

DR. PAUL F. WHITE (Dallas): I think most clinicians continue to use fentanyl because it appears to allow a smoother anesthetic, especially if you are performing a case with a face mask and not using muscle relaxants, a frequent occurrence in outpatients. It is very important to minimize the amount of opioid used. You are right in suggesting that even modest doses of fentanyl may increase the likelihood of nausea and vomiting in outpatients.

DR. PETER SEBEL (Atlanta): What is the essential difference among desflurane, isoflurane, and propofol, and how important is this difference?

DR. WHITE: I would suggest that studies to determine that to the fullest extent have not been conducted. For example, a study involving patients undergoing anesthesia with a face mask, which is, perhaps, 50% of our outpatient population, as far as I know, has not as yet been performed. The question is whether a less soluble agent like desflurane, with a presumed ability to improve titration, can equilibrate more rapidly and therefore provide better control. The problem with many studies, as you know, is that we are required to follow rather rigid protocols (deemed necessary to comply with FDA requirements) that do not reflect the way in which we use the drugs clinically. Th other problem is that we have not performed sufficien outcome studies needed to evaluate the impact, not only i the early recovery period, but also how patients do afte discharge, on the way home, and once they have reache home. One would wonder whether an anesthetic with much reduced solubility might offer advantages in terms o effects that occur hours later.

DR. SEBEL: Our study patients came back at 24 h to repea the battery of tests again. There were no differences note between desflurane and isoflurane, and there were n apparent differences in subjective effects in any of them regardless of whether they had been given isoflurane o desflurane, with or without an intravenous inductio agent.

DR. EDMOND I. EGER II (San Francisco): With regard t the question of differences between animal and huma rates of recovery, you have implied, and correctly I think that the animals were not the recipients of other drugs tha might tend to normalize or equalize the two groups. I thin were we to look at pure desflurane or pure isoflurane i humans, we would see similar differences in humans a those seen in the animals. We are here presented with dat indicating that recovery is faster insofar as initial recovery i concerned, but long-term recovery has not been shown t be different. I would make some other observations wit regard to long-term recovery. First, there are several factor that influence recovery quite apart from anesthetic choice. Second, in the studies comparing desflurane with agent like isoflurane, the numerical averages indicated faster recovery with desflurane than with isoflurane, although there was no statistically significant difference in several studies. I would submit that the numbers involved in each of these studies are probably too small to achieve statistical significance if, indeed, there is a real difference, and it may take hundreds of patients rather than 20–40 patients per group to do that. Also, the ideal outpatient anesthetic might be one different from anything we have yet tested. For example, the ideal outpatient anesthetic might combine ketorolac, propofol, and desflurane, without nitrous oxide. This might be better, because the other drugs often used in outpatient anesthesia, including nitrous oxide, thiopental, and narcotics, may precipitate nausea and vomiting.

DR. WHITE: I think there are dangers in combining data from multicenter studies (to assemble a larger sample) because there are other confounding factors that could influence those results. The early desflurane studies were not designed to rigorously evaluate early recovery or discharge. Also important is consideration of how patients feel postoperatively. If it turns out that desflurane-treated patients are less depressed, less lethargic, feel better in the early recovery period, and can be mobilized sooner, then we will have rapid acceptance of this as an alternative to isoflurane. One cannot lose sight of the fact that the comparator for desflurane is really isoflurane, not propofol.

DR. ROBERT G. MERIN (Houston): I have a question for Dr. Eger. In his summation about nitrous oxide a few years ago, he decided that nitrous oxide was not a causative agent in postoperative nausea and vomiting, generally speaking. Is this different now for desflurane? Do you feel that it is a causative agent with desflurane?

DR. EGER: I definitely believe that nitrous oxide causes nausea; in fact, I know it causes nausea and vomiting, because I can produce nausea in the volunteers that we study, in 80%–90% of them, just by giving them 40%–60% nitrous oxide with no other agent. They vomit, and they vomit repeatedly. In the nitrous oxide data that we published from a series of studies, we did say that it was difficult to see differences with versus without nitrous oxide, although in one group we did show differences, particularly in young patients who received nitrous oxide for a particular procedure.

DR. R. D. MILLER: Are you talking about nausea and vomiting during induction of anesthesia, or recovery, or both?

DR. EGER: Both. If you look at the desflurane studies and at the comparisons between the patients who received nitrous oxide versus those who did not (i.e., who received desflurane and oxygen), there is a rather striking difference in the incidence of nausea and vomiting.

DR. MERIN: To me, the problem is producing analgesia without increasing nausea and vomiting.

DR. CHARLES H. McLESKY (Denver): In pediatrics we seldom use narcotics. Probably 70% of our patients are outpatients. We administer an inhaled agent and a long-acting local anesthetic for postoperative analgesia. The vast majority of our children never receive a narcotic. When we participated in this multiinstitutional study, we attempted to see whether there was any difference between recovery in our patients, and we intentionally interfaced some protocols. The end result was that recovery from desflurane was faster than halothane. It was 6.7 min for eye opening versus, I think, 9.1 min for halothane. Return of corneal reflex and of conjugate gaze from disconjugate gaze was also more rapid in the desflurane group than in the halothane group. Discharge from recovery and from the hospital were not different. We called all the parents the next day to find out how the children did with nausea and vomiting, and the incidence was the same in both groups at 24 h. Many children get sick in the car on the way home. So I agree that you should look at 24 h, not just the first few hours after an anesthetic. I think more studies are needed that do look at pure techniques, where you are using just an inhaled agent and a local anesthetic, without narcotics. I think that will help clear some of the confusion about rapidity of wake-up and the nausea and vomiting issues, as well.

DR. WHITE: If you can minimize opioid administration, you can decrease nausea and vomiting. The ability to use a potent inhaled agent as the primary anesthetic may be advantageous.

DR. PETER GLASS (Durham): It would appear from a pharmacokinetic point of view that when you compare isoflurane with desflurane for 1-h procedures, you should see only a small difference in terms of recovery. As you extend procedure times—1, 3, 4 h—this difference will become more and more apparent. Do you agree?

DR. WHITE: Past comparisons between isoflurane and enflurane have demonstrated that differences only became apparent after 60 min. In fact, most of those studies indicated that unless the anesthetic is at least 90 min in duration, it was hard to show any advantage of isoflurane over enflurane. Actually, for very short cases enflurane tends to have a somewhat shorter recovery time despite its greater solubility. Whether this will hold for the isoflurane versus desflurane comparison is not known.

DR. STEPHEN ROBINSON (Portland): When you look at efficiency, what can you save in costs with an anesthetic? Discharge home is one criterion. Discharge from recovery room is often important. Ease of care in the recovery room is also a criterion to predict staffing requirements. A higher incidence of immediate postoperative nausea and vomiting will necessitate higher staffing levels. In doing brief cases, the operating room turnover rate becomes a critical step in keeping operating costs low. We (anesthesia) are usually the limiting step, and if it takes even 3–5 min longer to wake a patient up or to no longer have to attend to them in the recovery room, we are responsible for the incremental increase in time in that room. As we look toward specific cases, trying to identify what characteristics of desflurane make a difference, I think it is going to be very important to consider these elements.

ANESTHESIA & ANALGESIA

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A LOGICAL CHOICE

CRUCIAL PARAMETERS IN SELECTING A NEUROMUSCULAR BLOCKING AGENT

	Norcuron® (vecuronium bromide) for injection	Atracurium besylate
HEMODYNAMICS	No significant variations in blood pressure, cardiac output, or systemic vascular resistance.[1]	Statistically significant variations in blood pressure, cardiac output, and systemic vascular resistance.[1] ($P<.05$)
HISTAMINE	Available clinical experience indicates that reactions commonly associated with histamine release are unlikely to occur.[1-4]	Precautions advised for patients in whom substantial histamine release would be hazardous (eg, clinically significant cardiovascular disease, asthma).[5]
RECOVERY To 25% of control To 95% of control	 25-40 min[3] 45-65 min[3]	 35-45 min[5] 60-70 min[5]
DOSING FLEXIBILITY	The initial recommended dose is 0.08-0.1 mg/kg. Dose can be increased up to 0.28 mg/kg for long cases without significant histamine release or related cardiovascular side effects.[1,3,4]	Initial recommended dose is 0.4-0.5 mg/kg. A moderate histamine release and significant falls in blood pressure have been seen following a dose of 0.5 mg/kg ($P<.05$) and 0.6 mg/kg.[*2,5,6]
STORAGE & SHELF LIFE	2-year shelf life in lyophilized form at room temperature.[†] Can be reconstituted with various IV solutions including Lactated Ringers.[‡]	2-year shelf life under constant refrigeration.[†] Upon removal from refrigeration to room temperature storage, use within 14 days even if rerefrigerated.[5]

[*] Dose of atracurium above 0.5 mg/kg is not recommended.
[†] As originally supplied by the respective manufacturers.
[‡] Storage after reconstitution varies with solution. See package insert.

Norcuron®
(vecuronium bromide) for injection

A LOGICAL CHOICE FOR NEUROMUSCULAR BLOCKADE

See following page for brief summary of prescribing information.

Organon

ORGANON INC.
WEST ORANGE
NEW JERSEY 07052

Norcuron®

(vecuronium bromide) for injection

Before prescribing, please consult complete product information, a summary of which follows:

> **THIS DRUG SHOULD BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS.**

CONTRAINDICATIONS: Norcuron® is contraindicated in patients known to have a hypersensitivity to it.

WARNINGS: NORCURON® SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION. TO REDUCE THE POSSIBILITY OF PROLONGED NEUROMUSCULAR BLOCKADE AND OTHER POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING LONG-TERM USE IN THE ICU, NORCURON® OR ANY OTHER NEUROMUSCULAR BLOCKING AGENT SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSES BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH ITS ACTIONS AND WHO ARE FAMILIAR WITH APPROPRIATE PERIPHERAL NERVE STIMULATOR MUSCLE MONITORING TECHNIQUES (see PRECAUTIONS). In patients who are known to have myasthenia gravis or the myasthenic (Eaton-Lambert) syndrome, small doses of Norcuron® may have profound effects. In such patients, a peripheral nerve stimulator and use of a small test dose may be of value in monitoring the response to administration of muscle relaxants.

PRECAUTIONS:

Renal Failure: Norcuron® is well tolerated without clinically significant prolongation of neuromuscular blocking effect in patients with renal failure who have been optimally prepared for surgery by dialysis. Under emergency conditions in anephric patients some prolongation of neuromuscular blockage may occur; therefore, if anephric patients cannot be prepared for non-elective surgery, a lower initial dose of Norcuron® should be considered.

Altered Circulation Time: Conditions associated with slower circulation time in cardiovascular disease, old age, edematous states resulting in increased volume of distribution may contribute to a delay in onset time, therefore dosage should not be increased.

Hepatic Disease: Limited experience in patients with cirrhosis or cholestasis has revealed prolonged recovery time in keeping with the role the liver plays in Norcuron® metabolism and excretion. Data currently available do not permit dosage recommendations in patients with impaired liver function.

Long-term Use in I.C.U.: In the intensive care unit, in rare cases, long-term use of neuromuscular blocking drugs to facilitate mechanical ventilation may be associated with prolonged paralysis and/or skeletal muscle weakness that may be first noted during attempts to wean such patients from the ventilator. Typically, such patients receive other drugs such as broad spectrum antibiotics, narcotics and/or steroids and may have electrolyte imbalance and diseases which lead to electrolyte imbalance, hypoxic episodes of varying duration, acid-base imbalance and extreme debilitation, any of which may enhance the actions of a neuromuscular blocking agent. Additionally, patients immobilized for extended periods frequently develop symptoms consistent with disuse muscle atrophy. The recovery picture may vary from regaining movement and strength in all muscles to initial recovery of movement of the facial and small muscles of the extremities then to the remaining muscles. In rare cases recovery may be over an extended period of time and may even, on occasion, involve rehabilitation. Therefore, when there is a need for long-term mechanical ventilation, the benefits-to-risk ratio of neuromuscular blockade must be considered. Continuous infusion or intermittent bolus dosing to support mechanical ventilation has not been studied sufficiently to support dosage recommendations.

IN THE INTENSIVE CARE UNIT, APPROPRIATE MONITORING, WITH THE USE OF A PERIPHERAL NERVE STIMULATOR TO ASSESS THE DEGREE OF NEUROMUSCULAR BLOCKADE, IS RECOMMENDED TO HELP PRECLUDE POSSIBLE PROLONGATION OF THE BLOCKADE. WHENEVER THE USE OF NORCURON® OR ANY NEUROMUSCULAR BLOCKING AGENT IS CONTEMPLATED IN THE ICU, IT IS RECOMMENDED THAT NEUROMUSCULAR TRANSMISSION BE MONITORED CONTINUOUSLY DURING ADMINISTRATION AND RECOVERY WITH THE HELP OF A NERVE STIMULATOR. ADDITIONAL DOSES OF NORCURON® OR ANY OTHER NEUROMUSCULAR BLOCKING AGENT SHOULD NOT BE GIVEN BEFORE THERE IS A DEFINITE RESPONSE TO T_1 OR TO THE FIRST TWITCH. IF NO RESPONSE IS ELICITED, INFUSION ADMINISTRATION SHOULD BE DISCONTINUED UNTIL A RESPONSE RETURNS.

Severe Obesity or Neuromuscular Disease: Patients with severe obesity or neuromuscular disease may pose airway and/or ventilatory problems requiring special care before, during and after the use of neuromuscular blocking agents such as Norcuron®.

Malignant Hyperthermia: Many drugs used in anesthetic practice are suspected of being capable of triggering a potentially fatal hypermetabolism of skeletal muscle known as malignant hyperthermia. There are insufficient data derived from screening in susceptible animals (swine) to establish whether or not Norcuron® is capable of triggering malignant hyperthermia.

C.N.S.: Norcuron® has no known effect on consciousness, the pain threshold or cerebration. Administration must be accompanied by adequate anesthesia or sedation.

Drug Interactions: Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron® (vecuronium bromide) for injection and its duration of action. If succinylcholine is used before Norcuron®, the administration of Norcuron® should be delayed until the succinylcholine effect shows signs of wearing off. With succinylcholine as the intubating agent, initial doses of 0.04-0.06 mg/kg of Norcuron® may be administered to produce complete neuromuscular block with clinical duration of action of 25-30 minutes. The use of Norcuron® before succinylcholine, in order to attenuate some of the side effects of succinylcholine, has not been sufficiently studied.

Other nondepolarizing neuromuscular blocking agents (pancuronium, d-tubocurarine, metocurine, and gallamine) act in the same fashion as does Norcuron®, therefore these drugs and Norcuron® may manifest an additive effect when used together. There are insufficient data to support concomitant use of Norcuron® and other competitive muscle relaxants in the same patient.

Inhalational Anesthetics: Use of volatile inhalational anesthetics such as enflurane, isoflurane, and halothane with Norcuron® will enhance neuromuscular blockade. Potentiation is most prominent with use of enflurane and isoflurane. With the above agents the initial dose of Norcuron® may be the same as with balanced anesthesia unless the inhalational anesthetic has been administered for a sufficient time at a sufficient dose to have reached clinical equilibrium.

Antibiotics: Parenteral/intraperitoneal administration of high doses of certain antibiotics may intensify or produce neuromuscular block on their own. The following antibiotics have been associated with various degrees of paralysis: aminoglycosides (such as neomycin, streptomycin, kanamycin, gentamicin, and dihydrostreptomycin); tetracyclines; bacitracin; polymyxin B; colistin; and sodium colistimethate. If these or other newly introduced antibiotics are used in conjunction with Norcuron®, unexpected prolongation of neuromuscular block should be considered a possibility.

Other: Experience concerning injection of quinidine during recovery from use of other muscle relaxants suggest that recurrent paralysis may occur. This possibility must also be considered for Norcuron®. Norcuron® induced neuromuscular blockade has been counteracted by alkalosis and enhanced by acidosis in experimental animals (cat). Electrolyte imbalance and diseases which lead to electrolyte imbalance, such as adrenal cortical insufficiency, have been shown to alter neuromuscular blockade. Depending on the nature of the imbalance, either enhancement or inhibition may be expected. Magnesium salts, administered for the management of toxemia of pregnancy, may enhance the neuromuscular blockade.

Drug/laboratory test interactions: None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential or impairment of fertility.

Pregnancy: Pregnancy Category C: Animal reproduction studies have not been conducted with Norcuron®. It is also not known whether Norcuron® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Norcuron® should be given to a pregnant woman only if clearly needed.

Pediatric Use: Infants under 1 year of age but older than 7 weeks, also tested under halothane anesthesia, are moderately more sensitive to Norcuron® on a mg/kg basis than adults and take about 1½ times as long to recover. Information presently available does not permit recommendations for usage in neonates.

ADVERSE REACTIONS: The most frequent adverse reaction to nondepolarizing blocking agents as a class consists of an extension of the drug's pharmacological action beyond the time period needed. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiration insufficiency or apnea.

Inadequate reversal of the neuromuscular blockade is possible with Norcuron® as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate. Little or no increase in intensity of blockade or duration of action of Norcuron® is noted from the use of thiobarbiturates, narcotic analgesics, nitrous oxide, or droperidol. See OVERDOSAGE for discussion of other drugs used in anesthetic practice which also cause respiratory depression.

Prolonged to profound extensions of paralysis and/or muscle weakness as well as muscle atrophy have been reported after long-term use to support mechanical ventilation in the intensive care unit (see PRECAUTIONS).

The administration of Norcuron® has been associated with rare instances of hypersensitivity reactions (bronchospasm, hypotension and/or tachycardia, sometimes associated with acute urticaria or erythema).

OVERDOSAGE: The possibility of iatrogenic overdosage can be minimized by carefully monitoring muscle twitch response to peripheral nerve stimulation.

Excessive doses of Norcuron® produce enhanced pharmacological effects. Residual neuromuscular blockage beyond the time period needed may occur with Norcuron® as with other neuromuscular blockers. This may be manifested by skeletal muscle weakness, decreased respiratory reserve, low tidal volume, or apnea. A peripheral nerve stimulator may be used to assess the degree of residual neuromuscular blockade from other causes of decreased respiratory reserve.

Respiratory depression may be due either wholly or in part to other drugs used during the conduct of general anesthesia such as narcotics, thiobarbiturates and other central nervous system depressants. Under such circumstances, the primary treatment is maintenance of a patent airway and manual or mechanical ventilation until complete recovery of normal respiration is assured. Regonol® (pyridostigmine bromide) injection, neostigmine, or edrophonium, in conjunction with atropine or glycopyrrolate will usually antagonize the skeletal muscle relaxant action of Norcuron®. Satisfactory reversal can be judged by adequacy of skeletal muscle tone and by adequacy of respiration. A peripheral nerve stimulator may also be used to monitor restoration of twitch height. Failure of prompt reversal (within 30 minutes) may occur in the presence of extreme debilitation, carcinomatosis, and with concomitant use of certain broad spectrum antibiotics, or anesthetic agents and other drugs which enhance neuromuscular blockade or cause respiratory depression of their own. Under such circumstances the management is the same as that of prolonged neuromuscular blockade. Ventilation must be supported by artificial means until the patient has resumed control

DOSAGE AND ADMINISTRATION: Before prescribing, please consult complete product information. Norcuron® (vecuronium bromide) for injection is for intravenous use only. This drug should be administered by or under the supervision of experienced clinicians familiar with the use of neuromuscular blocking agents. Dosage must be individualized in each case. dosage information which follows is derived from studies based upon units of drug per unit of body weight and is intended t serve as a guide only, especially regarding enhancement of neuromuscular blockade of Norcuron® by volatile anesthetics an by prior use of succinylcholine (see PRECAUTIONS/Drug Interactions). Parenteral drug products should be inspected visuall for particulate matter and discoloration prior to administration whenever solution and container permit.

To obtain maximum clinical benefits of Norcuron® and to minimize the possibility of overdosage, the monitoring of musc twitch response to peripheral nerve stimulation is advised.

The recommended initial dose of Norcuron® is 0.08 to 0.10 mg/kg (1.4 to 1.75 times the ED_{90}) given as an intravenous bo injection. This dose can be expected to produce good or excellent non-emergency intubation conditions in 2.5 to 3 minutes after injection. Under balanced anesthesia, clinically required neuromuscular blockade lasts approximately 25-30 minutes. w recovery to 25% of control achieved approximately 25 to 40 minutes after injection and recovery to 95% of control achieved approximately 45-65 minutes after injection. In the presence of potent inhalation anesthetics, the neuromuscular blocking eff of Norcuron® is enhanced. If Norcuron® is first administered more than 5 minutes after the start of inhalation agent or when steady state has been achieved, the initial Norcuron® dose may be reduced by approximately 15%, i.e., 0.060 to 0.085 mg/k

Prior administration of succinylcholine may enhance the neuromuscular blocking effect and duration of action of Norcuro If intubation is performed using succinylcholine, a reduction of initial dose of Norcuron® to 0.04-0.06 mg/kg with inhalation anesthesia and 0.05-0.06 mg/kg with balanced anesthesia may be required.

During prolonged surgical procedures, maintenance doses of 0.010 to 0.015 mg/kg of Norcuron® are recommended; after initial Norcuron® injection, the first maintenance dose will generally be required within 25 to 40 minutes. However, clinical cr ria should be used to determine the need for maintenance doses. Since Norcuron® lacks clinically important cumulative effe subsequent maintenance doses, if required, may be administered at relatively regular intervals for each patient, ranging appro imately from 12 to 15 minutes under balanced anesthesia, slightly longer under inhalation agents. (If less frequent administration is desired, higher maintenance doses may be administered.)

Should there be reason for the selection of larger doses in individual patients, initial doses ranging from 0.15 mg/kg up to 0.28 mg/kg have been administered during surgery under halothane anesthesia without ill effects to the cardiovascular syste being noted as long as ventilation is properly maintained.

Use by Continuous Infusion: After an intubating dose of 80-100 µg/kg, a continuous infusion of 1 µg/kg/min can be ini ated approximately 20-40 min later. Infusion of Norcuron® should be initiated only after early evidence of spontaneous reco from the bolus dose. Long-term intravenous infusion to support mechanical ventilation in the intensive care unit has not bee studied sufficiently to support dosage recommendations (see PRECAUTIONS).

The infusion of Norcuron® should be individualized for each patient. The rate of administration should be adjusted accord to the patient's twitch response as determined by peripheral nerve stimulation. An initial rate of 1 µg/kg/min is recommende with the rate of the infusion adjusted thereafter to maintain a 90% suppression of twitch response. Average infusion rates ma range from 0.8 to 1.2 µg/kg/min.

Inhalation anesthetics, particularly enflurane and isoflurane may enhance the neuromuscular blocking action of nondepolarizing muscle relaxants. In the presence of steady-state concentrations of enflurane or isoflurane, it may be necessary reduce the rate of infusion 25-60 percent, 45-60 min after the intubating dose. Under halothane anesthesia it may not be necessary to reduce the rate of infusion.

Spontaneous recovery and reversal of neuromuscular blockade following discontinuation of Norcuron® infusion may be expected to proceed at rates comparable to that following a single bolus dose.

Infusion solutions of Norcuron® can be prepared by mixing Norcuron® with an appropriate infusion solution such as 5% glucose in water, 0.9% NaCl, 5% glucose in saline, or Lactated Ringers. Unused portions of infusion solutions should be discarded.

Infusion rates of Norcuron® can be individualized for each patient using the following table:

Drug Delivery Rate (µg/kg/min)	Infusion Delivery Rate (mL/kg/min)	
	0.1 mg/mL*	0.2 mg/mL†
0.7	0.007	0.0035
0.8	0.008	0.0040
0.9	0.009	0.0045
1.0	0.010	0.0050
1.1	0.011	0.0055
1.2	0.012	0.0060
1.3	0.013	0.0065

*10 mg of Norcuron® in 100 mL solution †20 mg of Norcuron® in 100 mL solution

The following table is a guideline for mL/min delivery for a solution of 0.1 mg/mL (10 mg in 100 mL) with an infusion pump.

NORCURON® INFUSION RATE – mL/MIN

Amount of Drug µg/kg/min	Patient Weight – kg						
	40	50	60	70	80	90	100
0.7	0.28	0.35	0.42	0.49	0.56	0.63	0.70
0.8	0.32	0.40	0.48	0.56	0.64	0.72	0.80
0.9	0.36	0.45	0.54	0.63	0.72	0.81	0.90
1.0	0.40	0.50	0.60	0.70	0.80	0.90	1.00
1.1	0.44	0.55	0.66	0.77	0.88	0.99	1.10
1.2	0.48	0.60	0.72	0.84	0.96	1.08	1.20
1.3	0.52	0.65	0.78	0.91	1.04	1.17	1.30

NOTE: If a concentration of 0.2 mg/mL is used (20 mg in 100 mL), the rate should be decreased by one-half.

Dosage in Children: Older children (10 to 17 years of age) have approximately the same dosage requirements (mg/kg) as adults and may be managed the same way. Younger children (1 to 10 years of age) may require a slightly higher initial dose a may also require supplementation slightly more often than adults. Infants under one year of age but older than 7 weeks are moderately more sensitive to Norcuron® on a mg/kg basis than adults and take about 1½ times as long to recover. See also subsection of PRECAUTIONS titled Pediatric Use. Information presently available does not permit recommendation on usage neonates (see PRECAUTIONS). There are insufficient data concerning continuous infusion of vecuronium in children, therefor no dosing recommendation can be made.

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Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whe ever solution and container permit.

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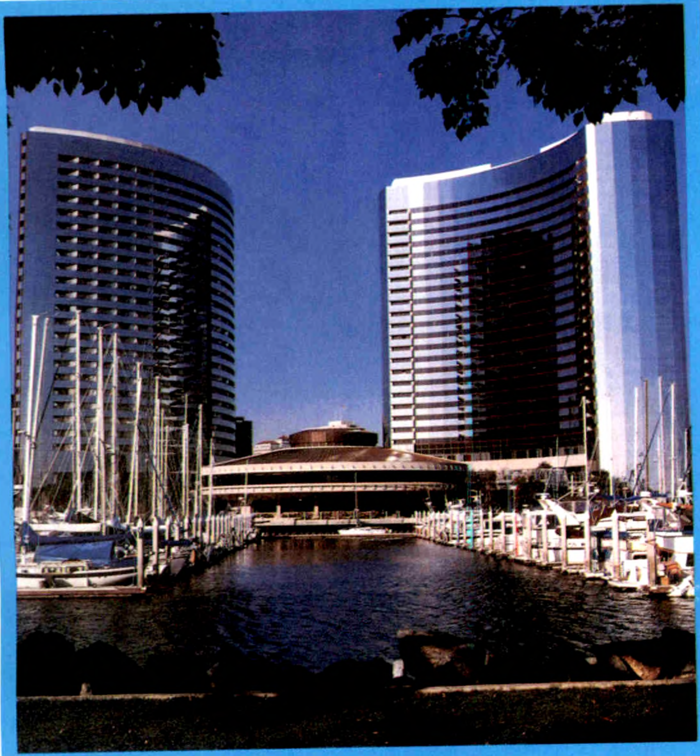

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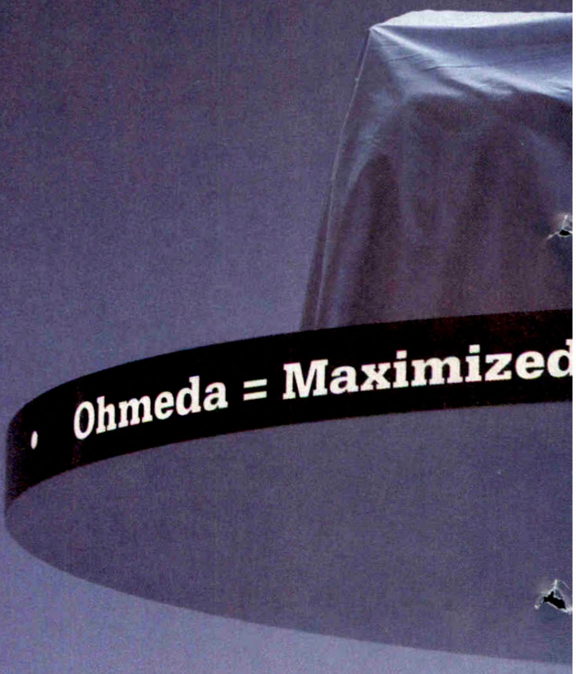

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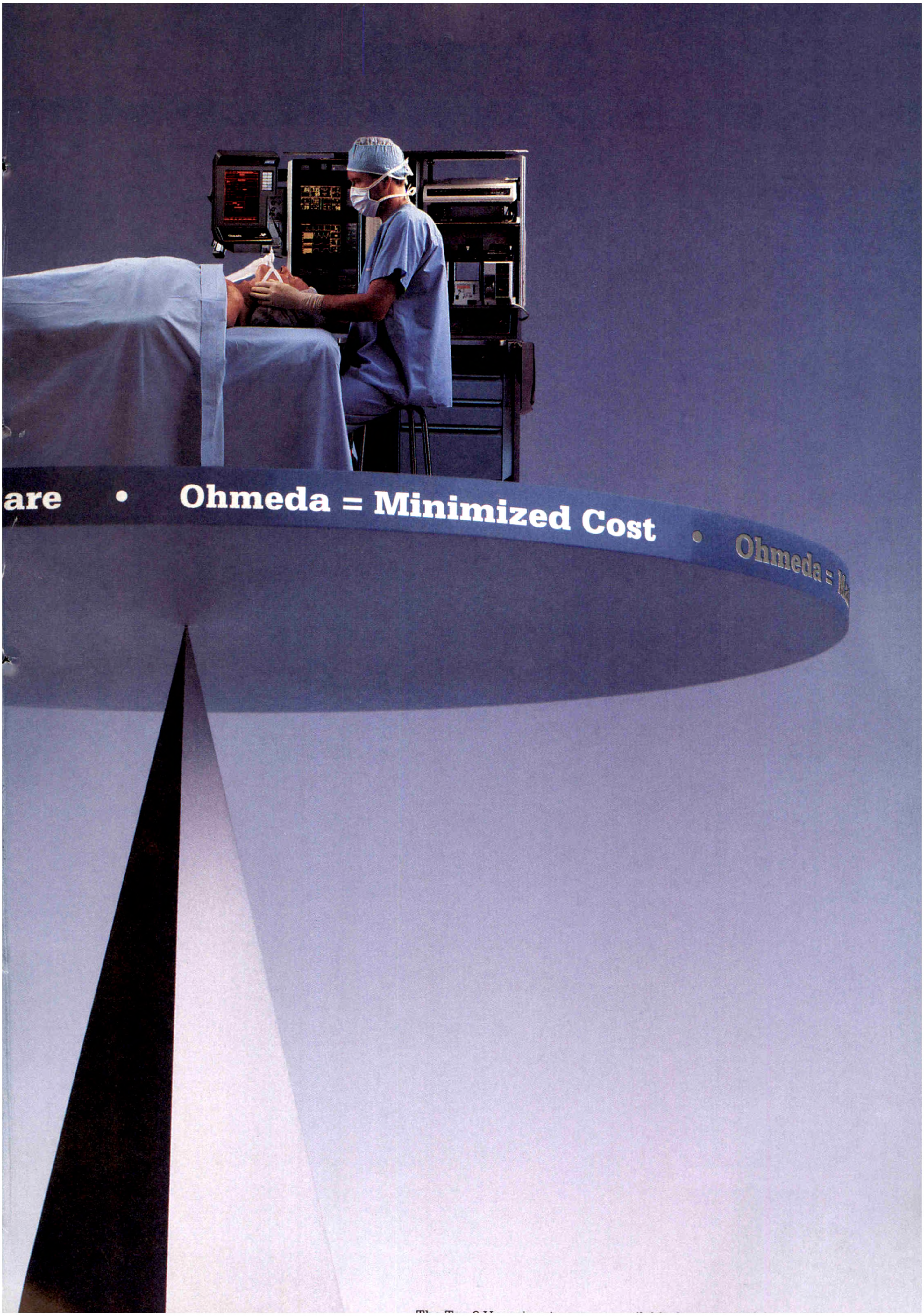
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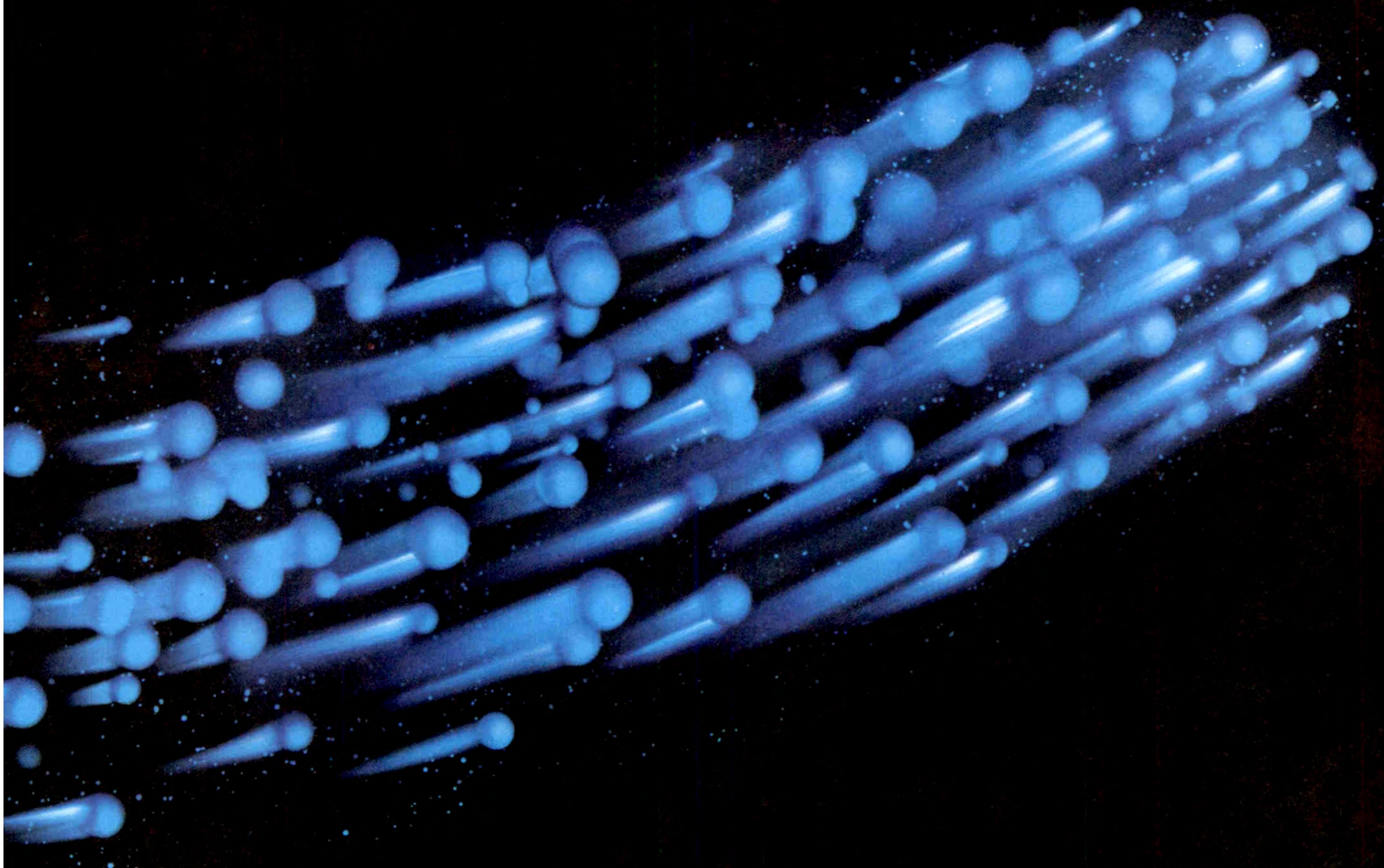

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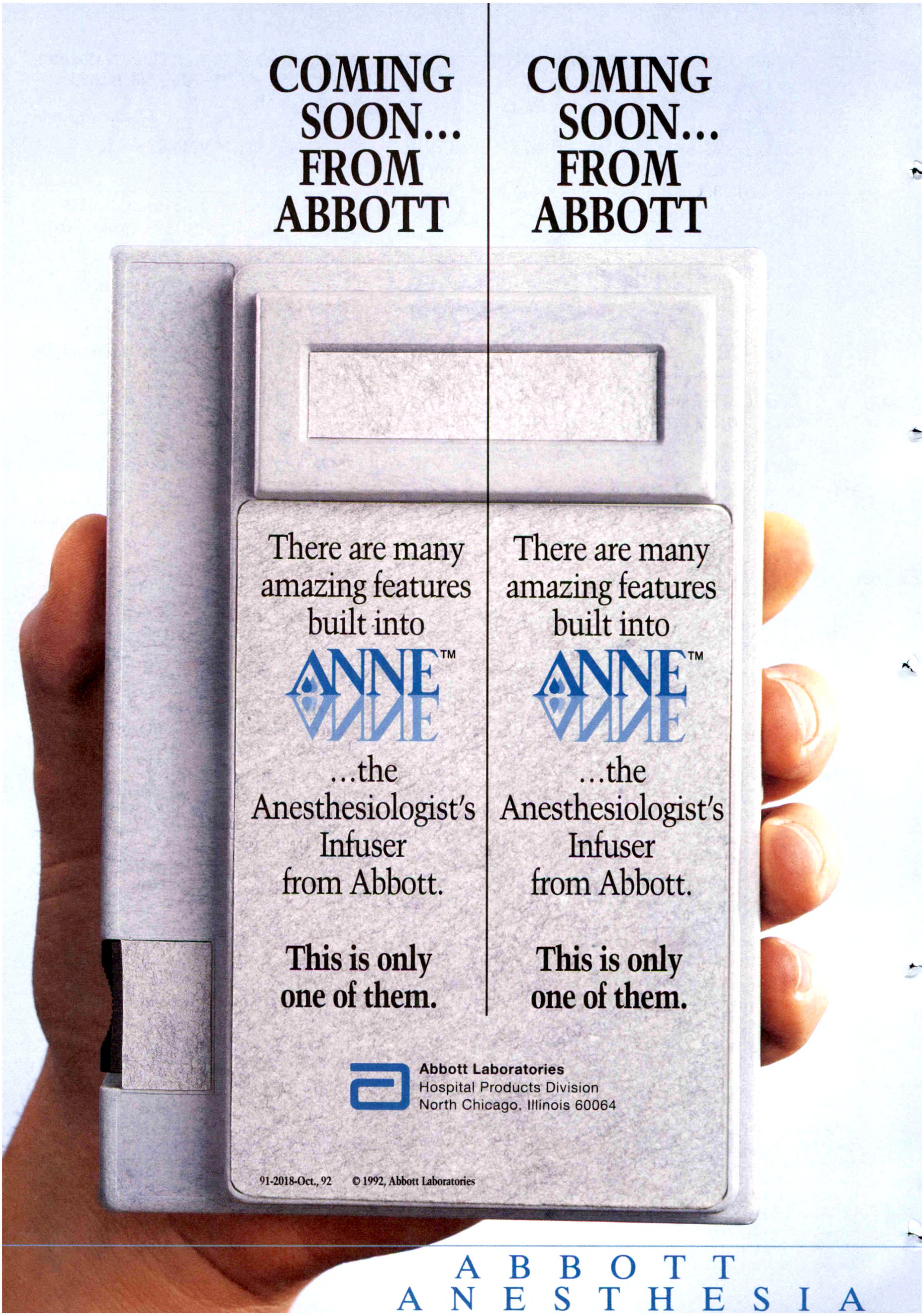

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EDITORIAL

Anemia, Hemodilution, and Oxygen Delivery

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The adequacy of oxygen delivery to all regions of the body is perhaps the best indicator of sufficient red cell mass and cardiac output. In the present issue of *Anesthesia & Analgesia*, van Woerkens and colleagues (1) present the unfortunate case of a patient who succumbed to perioperative complications, refusing transfusion therapy because of religious beliefs despite severe anemia. These authors obtained informed consent from this patient to study his oxygen delivery and consumption during profound normovolemic hemodilution. We are thus given a glimpse of this patient's physiologic responses to profound normovolemic hemodilution, with the conclusion that severe normovolemic hemodilution, to hemoglobin values as low as 4 g/dL, may be well tolerated in critically ill patients.

In this era of acquired immunodeficiency syndrome, hepatitis, cytomegalovirus, and other potential complications of homologous blood transfusion, this case, considered in isolation, may suggest that more aggressive normovolemic hemodilution strategies be used (i.e., less homologous blood transfusion). Van Woerkens et al. suggest a new "magic number," an oxygen delivery rate of 184 $mL \cdot m^{-2} \cdot min^{-1}$, as the critical value of oxygen delivery. Classically, a hematocrit of 30% has been recommended as optimal for the perioperative period (2–4). These recommendations were based primarily on theoretical calculations of maximal oxygen delivery to peripheral organs. Because blood viscosity is related to hematocrit in a curvilinear manner, moderate hemodilution may increase blood fluidity by decreasing viscosity and result in greater tissue flow, which more than compensates for the decreased blood oxygen content. Oxygen delivery may actually be increased. Indeed, experimental data demonstrate that profound normovolemic hemodilution in otherwise healthy canines is well tolerated, with minimal complications and no evidence of impaired wound healing (5). Clinical studies have also observed no increased morbidity or mortality in patients with perioperative anemia (hematocrits of 20%–22%), even though limited oxygen extraction reserve may be present (6,7).

Cardiac function has had the most attention in the study of anemia. The myocardium extracts by far the largest percentage of oxygen, is virtually aerobic, has little metabolic reserve, and has a direct coupling (in most cases) between metabolism and myocardial function. It is the organ most easily studied and arguably the organ system most susceptible to anemia. Hemoglobin values <4 g/dL are associated with abnormal regional myocardial blood flow distribution in animals with normal coronary anatomy (8), yet profound perioperative hemodilution (to hemoglobin of 3 g/dL) was not associated with increased morbidity and mortality during pediatric cardiac surgery (9). There are conflicting reports on the effects of normovolemic anemia on myocardial function in the setting of experimental coronary artery disease (10–12). In general, moderate anemia may be tolerated in the setting of stable coronary disease, provided that circulating blood volume is maintained. These data were obtained in animals with normal left ventricular function. There is evidence that depressed left ventricular function may require a higher hematocrit (13). A recent report observed a higher incidence of postoperative myocardial ischemia in patients with a hematocrit <29% undergoing lower extremity revascularization (14), presumably with coexistent multisystem disease and impaired cardiac function.

Other organ systems appear to be less susceptible to the adverse effects of anemia, perhaps because their oxygen extraction is less than that of the myocardium. In fact, hemodilution may be of benefit in many disease states. Moderate hemodilution (hematocrit range 30%–35%) may ameliorate stroke damage if used within the first 6 h of cerebral insult (15,16). Moderate hemodilution also improves peripheral blood flow in occlusive vascular disease, most likely due to the improved fluid dynamics as a consequence of decreased blood viscosity (17). There is a suggestion that hemodilution may also protect against the consequences of renal ischemia (18). Tolerance to normovolemic anemia may allow more aggressive

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use of perioperative autologous blood harvesting, particularly in patients with significant coincident diseases who may benefit from perioperative anemia. Some preliminary evidence suggests that autologous blood harvesting before cardiopulmonary bypass, with subsequent infusion of this blood after cardiopulmonary bypass, results in improvement in coagulation status (19). There is little information with regard to possible pulmonary effects of hemodilution or the potential adverse effects of hemodilution in the setting of chronic obstructive pulmonary disease. Thus, normovolemic hemodilution may have potential benefits, even in high-risk patients.

No data have demonstrated the effects of transfusion therapy in reversing adverse effects of anemia. Preliminary evidence from our laboratory (20) and a recent clinical report (21) suggest that anemia-induced myocardial ischemia is readily reversed by minimal transfusion. Little is known with regard to the reversal of other anemia-induced effects. Had van Woerkens et al. (1) been able to apply transfusion therapy to their patient, it would have been of great interest to observe whether recovery of the relationship between oxygen delivery and oxygen consumption followed the identical curve or whether hysteresis of the curve (presumably the consequence of ischemia and relative "oxygen debt") required additional transfusion above the "magic number" of 184 $mL \cdot m^{-2} \cdot min^{-1}$ oxygen delivery to effect complete recovery. This point is certainly not moot or of mere scientific curiosity; hysteresis of the curve suggests incomplete recovery of oxygen delivery to offset oxygen consumption, making increased use of blood products mandatory to normalize oxygen consumption and presumably completely reverse the effects of anemia. Furthermore, hysteresis of the "anemia recovery curve" would discourage aggressive hemodilution or tolerance of moderate anemia, because inadequate oxygen delivery with resultant consequences of anemia would require more transfusions than had the threshold of inadequate delivery not been attained by prophylactic transfusion therapy.

The application of a universally accepted guideline on transfusion therapy is fraught with difficulties. Susceptibility of patients may be as individual as each patient, particularly with respect to coexistent pathology. Thus, it is unlikely that one specific number or value, be it hematocrit or oxygen delivery, will be able to be universally applied to all situations. It is more likely that certain patients may tolerate marked degrees of hemodilution without evidence of ischemia, myocardial or otherwise, whereas other patients may not tolerate even mild degrees of anemia. Some generalizations can be made, however. Patients with more serious medical problems may require higher hematocrit levels; Christopherson and colleagues (14) found an increased incidence of postoperative ischemia associated with hematocrits <29% in patients with peripheral vascular disease, and thus these investigators recommended a hematocrit of at least 29% to decrease the incidence of cardiac postoperative complications. Of note is that the effects of hemodilution on other organ systems, particularly the central nervous system, are not well defined; these potential benefits or risks to other organ systems need to be elucidated and put in perspective relative to cardiac risks of hemodilution.

The whole concept of anemia may need to be redefined in the 1990s, as we enter the era of artificial blood. Several promising compounds are now undergoing extensive testing, including genetically cloned human hemoglobin, pyridoxylated hemoglobin purified from outdated banked blood, and cross-linked bovine hemoglobin. All afford the prospect of decreasing whole-blood viscosity and improving microvascular blood flow while retaining some oxygen-carrying capacity. It remains to be seen what impact these compounds will have on transfusion practice, but if these compounds prove safe and effective, certainly this impact will be a major one. Thus, characterization of the effects of hemodilution and anemia on the cardiovascular system and other organ systems is crucial to our ability to effectively use both homologous transfusion therapy and artificial blood.

Teleologically, we appear to be "built to bleed," yet how much is too much? With organ system senescence or disease, particularly coronary artery disease, prudence may dictate maintenance of a higher hematocrit. However, although the risks of hemodilution-induced ischemia will be diminished with homologous transfusion, this therapy may result in other complications, such as blood-borne infections and transfusion-related complications. The risk of transfusion-acquired infections is significant, and immunosuppression, which can result in increased infection and cancer recurrence risks, should be seriously considered before transfusion therapy (22,23). In younger patients and in patients without significant organ system disease, profound hemodilution may impose a lesser risk compared with transfusion therapy, whereas older or more infirm persons may benefit more from transfusion.

Van Woerkens and colleagues (1) have given us a number on which to base further research. This "critical value" was obtained in one patient; generalization of therapy based on a single value in one patient to the population at large may be problematic, because the relationship between oxygen consumption and delivery may be idiosyncratic. Clinical applications based on their findings must be prudent, particularly in applying a global hemodynamic variable to clinical situations in which regional disease may exist in a large number of cases. Oxygen extraction rates vary markedly in different organ systems; it is unlikely that a global measure such as total body oxygen delivery/consumption can adequately predict the responses of specific organ systems to decreased oxygen delivery. It behooves our specialty to conduct careful, controlled clinical and laboratory research not only to define a reasonable endpoint for normovolemic hemodilution, but to characterize the global and regional responses to anemia and to examine the capacity of transfusion therapy with autologous, homologous, or artificial blood to reverse the complications of anemia.

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Effect of Preoperative Normovolemic Hemodilution on Left Ventricular Segmental Wall Motion During Abdominal Aortic Surgery

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Preoperative normovolemic hemodilution (PNH) has been proposed for patients scheduled to undergo aortic surgery. Coronary artery disease is frequent in these patients. The aim of the study was to assess the effect of PNH on hemodynamics and segmental wall motion (SWM) evaluated by transesophageal echocardiography in such patients. Twenty patients with coronary artery disease were allocated randomly to either PNH or no PNH; PNH was performed after anesthetic induction using dextran 60,000. Patients were operated on under general anesthesia and monitored intraoperatively with electrocardiographic lead CM_5, radial and pulmonary artery catheters, and transesophageal echocardiography positioned to obtain a short-axis view. Hemodynamic and transesophageal echocardiographic data were collected after anesthetic induction and after PNH, before and 5 min after aortic clamping, after unclamping, and at the end of surgery. Aortic clamping induced a significant increase in systemic vascular resistance and arteriovenous difference in oxygen and a decrease in cardiac index ($P < 0.05$), but the effect of aortic clamping was inversely related to hemodilution. The SWM score (graded from 1 = normal to 5 = dyskinesia) was significantly increased after aortic clamping, mainly in the anterior segment ($P < 0.05$). Four patients in the control (no PNH) group and one in the PNH group developed new SWM abnormalities indicative of myocardial ischemia during surgery ($P =$ NS). This study suggests that PNH may improve hemodynamic tolerance to aortic clamping in patients with coronary artery disease. The observed changes in SWM indicate that PNH may not worsen myocardial ischemia in patients scheduled to undergo aortic surgery.

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Preoperative normovolemic hemodilution (PNH) has been proposed to avoid homologous blood transfusion in patients scheduled to undergo aortic surgery (1,2). Hemodilution decreases blood viscosity and may also improve oxygen delivery to tissues in these patients (3). However, patients who undergo abdominal aortic surgery frequently have coronary artery disease (CAD) (4), and CAD classically contraindicates PNH on the basis of results of experimental studies (5,6). Nevertheless, animal studies fail to document any significant negative effect of hemodilution on myocardial ischemia (7,8), and human studies do not in fact confirm the deleterious effect of PNH in patients with CAD. Laxenaire et al. (9) showed that in patients with CAD undergoing PNH for peripheral arterial disease, myocardial perfusion evaluated with thallium scintigraphy was not impaired. Recent studies performed during coronary artery bypass surgery showed that as much as 15% normovolemic hemodilution is well tolerated by the myocardium (10,11). Van der Linden et al. (12) showed that global myocardial function is preserved after PNH for abdominal aortic surgery (AAS). Patients undergoing AAS are likely to develop intraoperative myocardial ischemia and hemodynamic disturbances owing to clamping and unclamping of the aorta (13). Segmental wall motion (SWM) and wall-thickening abnormalities have been shown to be sensitive, early indices of myocardial ischemia, and transesophageal echocardiography (TEE) easily detects these changes (14). The current study was therefore conducted in such patients to assess the effect of PNH on hemodynamics and SWM during AAS, hypothesizing that PNH may not worsen myocardial ischemia.

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Methods

After approval by our hospital ethical committee and informed consent were obtained, all patients with CAD scheduled for infrarenal AAS were eligible for the study.

The diagnosis of CAD was made if the patient met at least one of the following criteria:

1. Presence of typical angina pectoris;
2. A documented previous myocardial infarction (Q waves on the ECG and increase in creatinine phosphokinase isoenzymes at the time of occurrence);
3. Ischemic ST segments (ST segment depression of 1.0 mm or ST segment elevation of 2.0 mm at 60 ms of the J point) or Q waves on the ECG;
4. A positive exercise treadmill test;
5. Fixed or reversible defect on dipyridamole thallium-201 angioscintigraphy;
6. Significant stenosis (>75%) of at least one main coronary artery on coronary arteriography.

Exclusion criteria were the absence of CAD as previously defined, a hematocrit <36%, or a history of recent congestive heart failure.

On the morning of operation, patients were randomly allocated to two groups: control (C) and hemodilution (H). All patients received their usual cardiac medications preoperatively, and 1 mg of flunitrazepam was administered 1 h before arrival in the operating room. In the operating room, standard monitors, including ECG lead CM_5, were applied. A thoracic epidural catheter was inserted with the patient in the sitting position via the T6–7 epidural space through a 19-gauge Tuohy needle for postoperative analgesia. Radial and pulmonary artery catheters were inserted under local anesthesia.

All patients had anesthesia induced with flunitrazepam (0.05 mg/kg) and alfentanil (30 μg/kg); tracheal intubation and muscle relaxation were obtained with vecuronium (0.8 mg/kg). Anesthesia was maintained with 50% N_2O in O_2 plus alfentanil infusion (30 $\mu g \cdot kg^{-1} \cdot h^{-1}$) and alfentanil (500–1000 μg) bolus doses as needed. Ventilation was controlled to maintain end-tidal CO_2 values of 30–35 mm Hg. A TEE 5-MHz probe (Vingmed) was then inserted and positioned to obtain a short-axis view at the midpapillary muscle level of the left ventricle.

Baseline data were collected for all patients 10 min after insertion of the TEE probe. Hemodilution was performed in group H and data were recorded 5 min after PNH was completed in this group only. Data were recorded for all the patients 5 min before and after aortic cross-clamping, 5 min after aortic unclamping, and at the end of surgery.

The TEE probe was removed at the completion of surgery, and the patients were transferred to the recovery room. Postoperative epidural pain management was started on arrival in the recovery room. All patients received a 2-mg bolus dose of morphine and 6 mL of 0.25% bupivacaine, followed by a continuous infusion of 0.125% bupivacaine (6 mL/h). Additional morphine bolus doses (2 mg in 10 mL of saline) were administered every 12 h for 3 days. The ECG and creatine kinase-MB data were collected every 12 h for 3 days.

Transesophageal Echocardiographic Data Analysis

The TEE data for each patient were analyzed on-line by the anesthesiologist in charge of the patient and a posteriori by an independent observer unaware of the patient's condition and hemodynamic profile during surgery. The left ventricle was arbitrarily divided into four segments for SWM analysis: anterior, posterior, inferior, and septal. The SWM was estimated using the following grading system (14): 1 = normal thickening and >30% segment shortening; 2 = mild hypokinesia (slightly reduced thickening and 10%–30% segment shortening); 3 = severe hypokinesia (<10% segment shortening and minimal thickening); 4 = akinesia (no thickening and no segment shortening); 5 = dyskinesia (wall thinning and no shortening of the segment). An increase of more than one grade, or a change from grade 4 to 5, was considered indicative of ischemia (14). Interobserver discrepancies defined as an SWM evaluation of more than one grade difference were resolved by a third experienced echocardiographer. During the postoperative period, ischemic events were defined by new Q waves or ischemic ST segment changes on ECG, by a creatinine kinase level >350 IU/mL, with a percentage of creatine kinase-MB >6%.

The PNH was performed after anesthetic induction before surgery. Blood withdrawal and compensation were done at the same time using two antebrachial venous 16-gauge catheters each inserted in a different arm. Final expected hematocrit was 30%. To achieve this, the volume of harvested blood was determined from initial hematocrit and body weight. All the hematocrits were measured by a cooximeter (Radiometer-Copenhagen, Denmark). The final hematocrit was verified and the hemodilution continued until the hematocrit reached 30%. Compensation was achieved using dextran 60,000 (Hemodex). Allergic reaction was prevented by the administration of 3 g of dextran 1000 (Promit). Dextran 60,000 infusion was restricted to <20 mL/kg to prevent modifications in coagulation time.

Table 1. Clinical Characteristics of the 20 Male Patients in the Two Study Groups and Results of Preoperative Cardiac Evaluation

Pt No./ Study group	Age (yr)	Height (cm)	Weight (kg)	Clinical course	ECG	Thallium	Coronary arteriography	Stress test
1/H	76	172	59	0	—	Inferior defect	—	—
2/H	76	165	68	Angina pectoris	—	Inferior reversible defect	Occluded RC artery	—
4/H	62	170	80	Inferior MI	Q II, III F	—	—	—
5/H	70	167	80	Anterior MI	Q I, II, III	Fixed anterior, reversible lateral defect		
9/H	71	180	80	Inferior MI	—	—	—	
10/H	65	170	75	Angina	—	Inferoanterior reversible defect	Stenosis >75% of the circumflex artery	Lateral ischemia
11/H	66	178	67	—	—	Anterolateral reversible defect	—	—
12/H	58	178	110	Angina	—		<75% distal stenosis (LAD artery)	—
14/H	71	167	71	Angina	—	—	Occluded LAD artery; LLD stenosis	—
17/H	56	170	78	—	—	Inferior reversible defect	RC artery stenosis	—
3/C	62	170	100	0		Lateral reversible defect	—	—
6/C	63	170	70	Inferior MI; unstable angina	Q III F	Inferior defect	—	—
7/C	79	170	78	Inferior MI	—	Inferoseptal defect	—	—
8/C	70	160	60	Anteroseptal MI	Q III F Q V 1,2,3	Apical defect	—	—
13/C	53	178	78	—	—	Anterior reversible defect	—	—
15/C	70	170	85	Inferior MI	—	—	—	Negative
16/C	58	156	72	—	—	Inferolateral defect	—	—
18/C	65	160	70	Angina	Q V 1,2,3	—	Occluded RC artery	—
19/C	76	178	63	[illegible]	—	Anterior reversible inferior fixed defect	—	—
20/C	66	160	84	CABG	ST V5 V6	—	—	—

C, control; CABG, coronary artery bypass graft; H, hemodilution; LAD, left anterior descending artery; LLD, left lateral descending artery; MI, myocardial infarction; Pt, patient; RC, right coronary artery.

Table 2. Mean Values of Homologous Transfusion and Blood Losses in the Two Study Groups

	Homologous transfusion (RBCP)	Blood loss (mL)
Group H		
Mean	0.9	1560
±SD	1.2	675
Group C		
Mean	1.4	910*
±SD	1.6	662

H, hemodilution; C, control; RBCP, red blood cell pack.
*$P < 0.05$, group C compared with group H.

The PNH lasted for 30 min. Normovolemia was controlled during PNH by the stability of pulmonary capillary wedge pressure (PCWP) and heart rate. The hematocrit and hemodynamics were recorded in the hemodilution (H) group 5 min after PNH. During the operation, if hemorrhage required transfusion, it was performed first with autologous and then with homologous blood.

Data Collection

Data collected during surgery included SWM and hemodynamics (i.e., systemic arterial pressure, pulmonary arterial pressure, PCWP, heart rate, and cardiac index [CI]). Arterial and mixed venous oxygen content, systemic vascular resistance (SVR) (normalized to the body surface area), and arteriovenous difference in oxygen were calculated from the measured variables. The volume of dextran infused and the amount of harvested blood evaluated from the number of collected red blood cell packs were noted. The TEE and hemodynamic measurements were performed 10 min after TEE insertion and anesthetic induction, at the end of PNH in group H, 5 min before and after aortic clamping, 5 min after aortic unclamping, and at the end of surgery in both study groups.

Table 3. Changes in Measured and Calculated Values of Hematocrit and Hemodynamic Variables in the Two Study Group

	Hct (%)	HR (beats/min)	PCWP (mm Hg)	SAP (mm Hg)	CI ($L \cdot min^{-1} \cdot m^{-2}$)	SVR (UI)	AVDO (vol%)
Baseline							
Group H	40 ± 3	55 ± 7	11 ± 4	76 ± 12	2.2 ± 0.5	31 ± 9	5.2 ± 1.0
Group C	40 ± 2	50 ± 8	11 ± 4	81 ± 14	2.5 ± 0.9	29 ± 8	5.3 ± 1.1
After hemodilution							
Group H	30 ± 2.7	57 ± 10	12 ± 3	76 ± 10	2.7 ± 0.8	25 ± 9	4.5 ± 0.7
Before clamping							
Group H	30 ± $3^{a,b}$	64 ± 16	13 ± 2	85 ± 7	3.2 ± 0.8^{a}	23 ± 6^{b}	3.3 ± 0.7
Group C	39 ± 3	54 ± 9	15 ± 4	92 ± 14	2.6 ± 0.6	31 ± 8	4.5 ± 1.3
After clamping							
Group H	27 ± $3^{a,b}$	60 ± 16	13 ± 4	85 ± 7	2.5 ± 0.7	31 ± 11^{b}	4.0 ± 0.9
Group C	37 ± 3	53 ± 11	12 ± 4	95 ± 14	2.0 ± 0.3^{a}	45 ± 13^{a}	5.5 ± 1.0
After unclamping							
Group H	29 ± $3^{a,b}$	60 ± 17	12 ± 5	83 ± 14	2.5 ± 0.5	30 ± 12	4.3 ± 0.8
Group C	37 ± 2.1	57 ± 13	11 ± 3	87 ± 15	2.7 ± 0.9	29 ± 7	4.8 ± 1.0
End							
Group H	29 ± $3.3^{a,b}$	62 ± 15	12 ± 4	86 ± 13	2.9 ± 0.4	26 ± 7	4.2 ± 0.1
Group C	38 ± 2	60 ± 12	11 ± 4	91 ± 10	2.7 ± 0.6	31 ± 5	4.5 ± 1.0

Hct, hematocrit; HR, heart rate; PCWP, pulmonary capillary wedge pressure; SAP, systemic arterial pressure; CI, cardiac index; SVR, systemic vascu resistance; $AVDO_2$, arteriovenous difference in oxygen; H, hemodilution; C, control.

Values presented as mean ± SD.

[a] $P < 0.05$ compared with baseline data.

[b] $P < 0.05$, intergroup comparison for hematocrit.

Statistics

Results are expressed as mean ± SD. Statistical analysis used a general mixed-model analysis of variance (BMDP software). Three variables were studied in the model for hemodynamics and SWM: hemodilution, patients, and time. $P < 0.05$ was considered significant. The number of ischemic events occurring in the two groups was compared by a Fischer exact test.

Results

The clinical characteristics of the 20 male patients included in this study are reported on Table 1. Mean age, height, and weight were, respectively, 67 ± 33 and 66 ± 7 yr, 160 ± 33 and 167 ± 8 cm, and 87 ± 34 and 76 ± 11 kg in groups H and C (P = NS). Intraoperative blood losses and infusions are reported in Table 2. In group H, 875 ± 273 mL of homologous blood was harvested and replaced by 1145 ± 391 mL of dextran solution. Blood losses were significantly greater in group H. Changes in hematocrit are reported in Table 3. During surgery, the mean hematocrit was always ≤30% in group H and >36% in group C ($P < 0.05$).

Peroperative hemodynamic changes are reported in Table 3. No significant difference was documented between the two groups of patients. Aortic clamping significantly changed CI, SVR, and arteriovenous difference in oxygen ($P < 0.05$), but heart rate, systemic arterial pressure, and PCWP were not modified. The general mixed-model analysis of variance allowed us to document an inverse relation between the effects hemodilution and aortic clamping on SVR and arteri venous difference in oxygen ($P < 0.05$).

Segmental Wall Motion Analysis

Four hundred segments were recorded, of which 3 could be analyzed. No discrepancy of more than or grade was noted between the two independent ol servers. A consensus was obtained in all the patien with the help of the third observer. The SWM mea scores are reported in Table 4. Segmental wall motic was significantly increased after clamping of tl abdominal aorta in the control group ($P < 0.05$). Tab 5 reports the scores of the patients (four patients an five segments in group C; one patient and or segment in group H; P = NS) who developed ne SWM abnormalities indicative of ischemia (tw grades). Except for one patient, abnormalities i SWM occurred after aortic clamping. One patient i group C documented ST segment depression aft aortic clamping, during which time, he develope severe hypokinesia (SWM score from 1 to 3) of tl anterior segment. The ECG and TEE abnormaliti disappeared after nitroglycerin infusion in this p tient, and TEE abnormalities were also corrected b nitroglycerin in the other patients, except for one i whom SWM hypokinesia persisted until the end surgery.

Postoperatively, no patient documented EC changes or an increase in creatine kinase-MB relate

Table 4. Mean Values of Segmental Wall Motion Scores in the Different Segments of the Left Ventricular Wall Documented by Transesophageal Echocardiography

Left ventricular wall segment	Baseline	Before aortic clamping	After aortic clamping	After aortic unclamping	End of surgery	*P* value
Anterior						
Group H	1.4 ± 1.2	1.6 ± 1.2	1.8 ± 1.2	1.7 ± 1.2	1.7 ± 1.3	NS
Group C	1.8 ± 1.3	1.9 ± 1.3	2.0 ± 1.2	1.7 ± 1.3	1.7 ± 1.2	NS
Lateral						
Group H	1.2 ± 0.4	1.0 ± 0	1.0 ± 0	1.1 ± 0.3	1.0 ± 0	NS
Group C	1.2 ± 0.4	1.4 ± 1.0	1.5 ± 0.9	1.1 ± 0.3	1.1 ± 0.3	NS
Inferior						
Group H	2.1 ± 1.3	1.8 ± 1.3	1.8 ± 1.2	1.9 ± 1.3	1.9 ± 1.3	NS
Group C	3.0 ± 1.5	2.9 ± 1.4	2.8 ± 1.6	3.0 ± 1.5	2.8 ± 1.6	NS
Septal						
Group H	1.7 ± 1.0	1.9 ± 0.9	1.9 ± 1.0	1.8 ± 0.9	1.7 ± 0.9	NS
Group C	2.4 ± 1.4	2.4 ± 1.3	2.7 ± 1.3	2.7 ± 1.3	2.5 ± 1.3	NS
All segments						
Group H	1.6 ± 1.1	1.5 ± 1.0	1.6 ± 1.0	1.6 ± 1.0	1.5 ± 1.0	
Group C	1.9 ± 1.3	2.0 ± 1.3	2.2 ± 1.3^a	2.0 ± 1.3	1.9 ± 1.3	

C, control; H, hemodilution; TEE, transesophageal echocardiography.
Values presented are mean ± SD.
^{a}$P < 0.05$, compared with baseline data.

Table 5. Segmental Wall Motion Scores in the Five Patients Who Documented Segmental Wall Motion Abnormalities During Surgery

Study group (Pt No.)	Left ventricular wall segment	Baseline	Before aortic clamping	After aortic clamping	After aortic unclamping	End of surgery
C (20)	Lateral	2	4	3	2	2
C (8)	Septal	1	1	3	3	3
C (7)	Anterior	1	1	3	1	1
C (10)	Lateral	1	1	3	1	1
C (18)	Anterior	1	1	3	1	1
H (14)	Septal	1	1	3	2	2

Pt, patient (see Table 1 for patient clinical characteristics); C, control; H, hemodilution.

to myocardial infarction. The late postoperative course was devoid of major complications in all the patients in this study.

Discussion

This study documents that PNH with dextran changes the hemodynamic profile of patients undergoing AAS and is associated with no important changes in SWM.

The typical hemodynamic response to aortic clamping is an increase in SVR associated with a decrease in CI (15). Changes in SVR depend on the development of the collateral circulation (16). Patients with aortoocclusive disease document less hemodynamic disturbances after aortic clamping, owing to the development of collateral bypass circulation. This study shows that changes in SVR after aortic cross-clamping are inversely related to hemodilution. Hemodilution has been previously documented to improve microvascular blood flow in some patients with peripheral vascular disease (17). In addition, hemodilution increases tissue perfusion and collateral circulation, especially when critical stenoses are developed (18,19). In this study, hemodilution may have increased blood flow through collateral circulation, even before aortic clamping, which would explain the lower values of calculated SVR before and after aortic clamping in group H.

The TEE analysis documented SWM abnormalities occurring especially after aortic cross-clamping. This result is apparently at variance with the study of Roizen et al. (20) who demonstrated that the majority of episodes of SWM abnormalities occurred after aortic declamping (20). In our study, intravenous infusion with dextran was carefully adapted to maintain PCWP, in order to reduce the changes in CI and systemic arterial pressure related to aortic unclamping. Consequently, these changes appeared to be minimal, explaining the lack of important abnormalities in SWM. Changes in SWM occurring after aortic cross-clamping might be related either to changes in loading conditions or to myocardial ischemia. Changes in left ventricular loading conditions could theoretically change SWM scores. An increase in afterload could cause normal segments to appear hypokinetic, so that abnormal segments would be overgraded. In this study, abnormalities in SWM occurring after aortic clamping were mainly located in only one segment and not in the complete ventricular wall. Therefore, they may be related more to myocardial ischemia than to global ventricular dysfunction.

Aortic cross-clamping may compromise the fragile myocardial oxygen balance by increasing myocardial oxygen demand. Because hemodynamic changes were less marked in the group H patients, this could explain why myocardial ischemia might occur less frequently in this group. In addition, PNH improves coronary capillary blood flow (7,21) and thus improves myocardial oxygen supply. Transesophageal echocardiography is considered a valuable technique for evaluation of myocardial ischemia (14,22), and its accuracy is better than conventional ECG (14). In this study, only one patient developed ST segment depression and SWM abnormalities simultaneously, confirming these findings.

Detection of SWM by TEE has some limitations, one of which is that hypokinesia has been suggested to be less specific than akinesia in detecting myocardial ischemia (23). Thus, in this study overestimation of myocardial ischemia may have occurred, but the error would be comparable in both groups.

Hemodilution is associated with an increase in blood loss that may be related to the effect of dextran on platelet function (24,25). This difference in blood loss explains why no significant difference in homologous blood requirement was documented in this study between the two groups.

We conclude that PNH is well tolerated in patients with CAD undergoing infrarenal AAS. Our results further suggest that PNH improves hemodynamic tolerance to aortic clamping and may decrease the incidence of myocardial ischemia.

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Splanchnic Hemodynamics and Oxygen Supply During Acute Normovolemic Hemodilution Alone and With Isoflurane-Induced Hypotension in the Anesthetized Pig

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Safety of combined hemodilution and isoflurane-induced hypotension was assessed by studying their effects on splanchnic hemodynamics and oxygenation in nine anesthetized (ketamine/flunitrazepam) pigs. Acute normovolemic hemodilution (decrease in hematocrit from 29% to 15%) with 6% hydroxyethyl starch decreased ($P < 0.05$) O_2 delivery despite increases in cardiac output and all splanchnic flows, as measured by electromagnetic flow probes. Superimposed isoflurane (1.45% end-tidal concentrations) caused marked decreases in arterial blood pressure, cardiac output, and splanchnic flows. Oxygen uptake of the liver became O_2 supply dependent. A liver surface Po_2 histogram (Clark-type electrode) showed 38% of Po_2 values between 0 and 5 mm Hg. Hepatic lactate uptake decreased by 75%. These data suggest that depression of cardiovascular function during reduced O_2-carrying capacity adversely affects hepatic perfusion, oxygenation, and function. Combined hemodilution and isoflurane-induced hypotension may not be appropriate in patients.

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Factors contributing to low preoperative hematocrit values in surgical patients include disease-related anemia, preoperative blood donation, and avoidance of blood transfusions for intravascular volume replacement. Transfusions are costly and carry a multitude of risks, including transfusion reactions, transmission of infection and disease, and possible immune suppression (1). Thus, alternatives to the use of homologous blood products are increasingly being sought (2,3). Preoperative acute normovolemic hemodilution (HD) and deliberate (controlled) hypotension are such alternatives (4,5).

One way of reducing arterial blood pressure during general anesthesia is the use of isoflurane. Systemic and regional hemodynamic responses to isoflurane have been studied extensively in the presence of a normal hematocrit (6–8). However, cardiovascular responses may differ substantially during underlying HD. In addition, coexistence of reduced O_2 content and perfusion pressure may well lead to tissue hypoxia. Thus, examination of the effects of combined HD and deliberately induced hypotension on regional organ perfusion and function are required before such a technique can be recommended for clinical practice.

Accordingly, the goal of this study was to evaluate first the effects of severe HD and, subsequently, of superimposed isoflurane-induced hypotension on systemic and, predominantly, hepatic perfusion, oxygenation, and metabolism. Although certain strains of pigs have baseline hematocrit values less than those of humans, the pig was chosen because of its anatomic and physiologic similarity to humans with respect to the cardiovascular and digestive systems (9).

Methods

Instrumentation

The experimental protocol was approved by the local Committee on Animal Research. The study was performed in nine 4–5-mo-old domestic male and female pigs, weighing 28–37 kg. After overnight fasting and intramuscular azoperon (5 mg/kg), anesthesia was induced with methomidate (6 mg/kg IV) administered via ear vein, and the trachea was intubated. Anesthesia was maintained by continuous intravenous infusions of ketamine ($4\ mg \cdot kg^{-1} \cdot h^{-1}$) and

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flunitrazepam (0.0125 $mg \cdot kg^{-1} \cdot h^{-1}$). Mechanical ventilation was provided by a constant-volume ventilator (Siemens, SV 900 B, Stockholm, Sweden) and facilitated by a continuous intravenous infusion of pancuronium (0.12 $mg \cdot kg^{-1} \cdot h^{-1}$). Respiratory rates and inspired O_2 concentration were adjusted to maintain arterial CO_2 tension between 38 and 42 mm Hg and arterial O_2 tension between 95 and 115 mm Hg. All animals were in the supine horizontal position. Body temperature was continuously monitored by a thermistor of a flow-directed thermodilution catheter (model 93A-131-7F, Edwards Laboratory) and was kept constant by placing the animals on a heating pad and by warming the inspired gases. Catheters were inserted into the abdominal aorta, pulmonary artery, and superior vena cava, as previously described (8). All animals received Ringer's solution at an amount (10–15 $mL \cdot kg^{-1} \cdot h^{-1}$) that maintained right and left cardiac filling pressures. After median laparotomy, the left hepatic and portal vein were cannulated, as previously described (8).

Precalibrated electromagnetic flow probes (Stölzer Messtechnik, Waldkirch, Germany) of appropriate sizes to ensure a snug fit were placed around the hepatic artery, portal vein, and superior mesenteric artery. Care was taken to preserve the periarterial nerve plexus. Zero flow readings were checked repeatedly during the experiment by transiently occluding the respective vessels.

Hemodynamic Measurements

Intravascular catheters were connected to pressure transducers (Senso Nor, type 840, Horten, Norway). A multichannel recorder (Hellige) was used for recording signals. Cardiac output was determined by thermodilution technique (Siemens, CO Computer model 404-1, Erlangen, Germany). The mean value of triplicate injections of 5 mL of ice-cold, temperature-monitored saline was considered to reflect actual cardiac output if the measurements were within a range of ±5% from the calculated mean.

Total hepatic blood flow was calculated as the sum of hepatic arterial and portal venous blood flow. Vascular resistances (systemic, hepatic arterial, portal venous, and superior mesenteric arterial) were calculated using the formulas listed in the Appendix. Heart rate was derived from the R-R intervals of an extremity electrocardiogram.

Determination of Oxygen Supply/Uptake

Blood gas tension and pH values were determined using an ABL 3 autoanalyzer (Radiometer, Copenhagen, Denmark). Hemoglobin O_2 saturation was measured by an OSM 3 hemoximeter (Radiometer). Hematocrit was measured from centrifuged (Bayer AG, Compur Microspin, Leverkusen, Germany) arterial blood sampled in capillary tubes. Hemoglobin concentration was determined by the cyan methemoglobin method. Oxygen content, delivery, uptake, and extraction ratios were derived from the formulas listed in the Appendix.

Preliminary studies had shown that there were no differences between portal and mesenteric venous O_2 content. Thus, portal venous O_2 content was used for the calculation of small intestine O_2 uptake (see Appendix).

Determination of Surface Po_2 of Liver and Small Intestine

Surface Po_2 of liver and small intestine were measured simultaneously using a multiwire platinum electrode, as described previously (10,11). Preliminary studies had shown that placement of the electrodes at different areas of the liver and small intestine surfaces produced comparable results. At each stage, a total of approximately 100 individual Po_2 measurements were obtained at 10–15 different electrode locations. The distribution of these values, illustrated as summary surface Po_2 histograms, reflects tissue oxygenation, which is the net result of nutritive blood flow and tissue O_2 consumption (12).

Determination of Hepatic Metabolic Function

Arterial, portal venous, and hepatic venous blood samples were collected for determination of lactate and pyruvate concentrations. These substances were determined enzymatically, as previously described (13). Hepatic uptake of lactate and pyruvate were calculated using formulas listed in the Appendix.

Experimental Protocol

At the end of the surgical preparation, at least 30 min was allowed before baseline readings during ketamine/flunitrazepam anesthesia were obtained. Hemodilution (with a mean hematocrit of 15%) was then induced by simultaneously replacing blood (withdrawn via right femoral artery) with roughly equal amounts of 6% hydroxyethyl starch (mol wt 450,000; Plasmasteril, Fresenius, Homburg, Germany) administered at body temperature via the left jugular vein. As indices of normovolemia, central venous and pulmonary capillary wedge pressures were maintained constant during the HD procedure. After the hematocrit had been decreased to the required level of 15%, measurements were performed after at least 15 min of stable hemodynamics.

Table 1. Variables for Systemic and Regional Hemodynamics During Baseline, Hemodilution, and Combined Hemodilution and Isoflurane in Anesthetized Pigs

Variable	Baseline	HD	HD + Iso
Intravascular pressure (mm Hg)			
Central venous	2.8 ± 0.4	2.8 ± 0.3	2.9 ± 0.5
Pulmonary capillary wedge	6.8 ± 0.4	6.7 ± 0.5	6.8 ± 0.5
Portal venous	6.9 ± 0.6	7.4 ± 0.6	7.1 ± 0.8
Hepatic venous	2.7 ± 0.4	2.9 ± 0.4	3.2 ± 0.6
Splanchnic blood flow (mL/min)			
Total hepatic	634 ± 24	864 ± 36^a	672 ± 56^b
Hepatic arterial	83 ± 6	149 ± 14^a	64 ± 9^{a,b}
Portal venous	561 ± 33	732 ± 45^a	616 ± 55^b
Superior mesenteric arterial	410 ± 31	492 ± 27^a	422 ± 32^b
Vascular resistance (U)			
Hepatic arterial	1142 ± 126	568 ± 55^a	618 ± 84^a
Portal venous	8 ± 2	6 ± 1^a	6 ± 1^a
Superior mesenteric arterial	220 ± 24	172 ± 31^a	74 ± 9^{a,b}

HD, hemodilution; Iso, isoflurane.
Values are mean ± SEM.
[a] $P < 0.05$, compared with baseline.
[b] $P < 0.05$, compared with HD.

Subsequently, isoflurane was introduced and maintained at an end-tidal concentration of 1.45% for 30–40 min. During administration of isoflurane, the infusion of ketamine was continued unchanged. Measurements were repeated during stable hemodynamics.

In four additional animals, after the surgical preparation, isoflurane (at an end-tidal concentration of 1.45%) was administered first, followed by HD (to a mean hematocrit of 15%). Data obtained after surgical preparation were compared with those obtained after HD during isoflurane. This was done to assess the likelihood of the sequence of experimental interventions (i.e., isoflurane always after HD) modifying the results.

In three additional animals, the effects of time on stability of surgical preparation during HD were evaluated. After surgical preparation and HD had been performed as described, measurements were obtained. Without any further intervention, repeat measurements were made 2 h later. None of the seven additional animals were studied in random order.

Statistical Analysis

The data were statistically analyzed by Friedman's statistic, followed by the Wilcoxon signed-rank test (for comparison between experimental periods), and by Kruskal-Wallis one-way analysis of variance, followed by the Mann-Whitney test (for comparisons within experimental periods). A P value of <0.05 was considered statistically significant. Values are presented as mean ± SEM.

Results

To reduce the hematocrit from an initial value of 29% ± 1% to 15% ± 1%, 33 ± 2 mL/kg of blood was withdrawn and replaced by 36 ± 2 mL/kg of 6% hydroxyethyl starch. At this exchange ratio, central venous and capillary wedge pressures remained unchanged (Table 1).

Systemic and Splanchnic Hemodynamics

Hemodilution resulted in increases in cardiac output and heart rate of approximately 20% and 30%, respectively (Figure 1). Stroke volume remained unchanged, mean arterial pressure decreased slightly (10%) but significantly, and systemic vascular resistance decreased by 35%.

Hemodilution caused increases in all splanchnic flows and decreases in regional vascular resistances (Table 1). When expressed as percent changes from baseline values, hepatic arterial blood flow increased (80%) more than twice as much as cardiac output and all other splanchnic flows (Figure 2). Correspondingly, hepatic arterial blood flow increased when expressed as a fraction of total hepatic blood flow (from 12% ± 1% to 17% ± 1%). The alterations in flows were reflected by quantitatively respective changes in vascular resistances (i.e., hepatic arterial greater than portal venous and superior mesenteric arterial) (Table 1).

During superimposed isoflurane, there were further decreases in mean arterial pressure (50%) and systemic vascular resistance (30%) and newly occur-

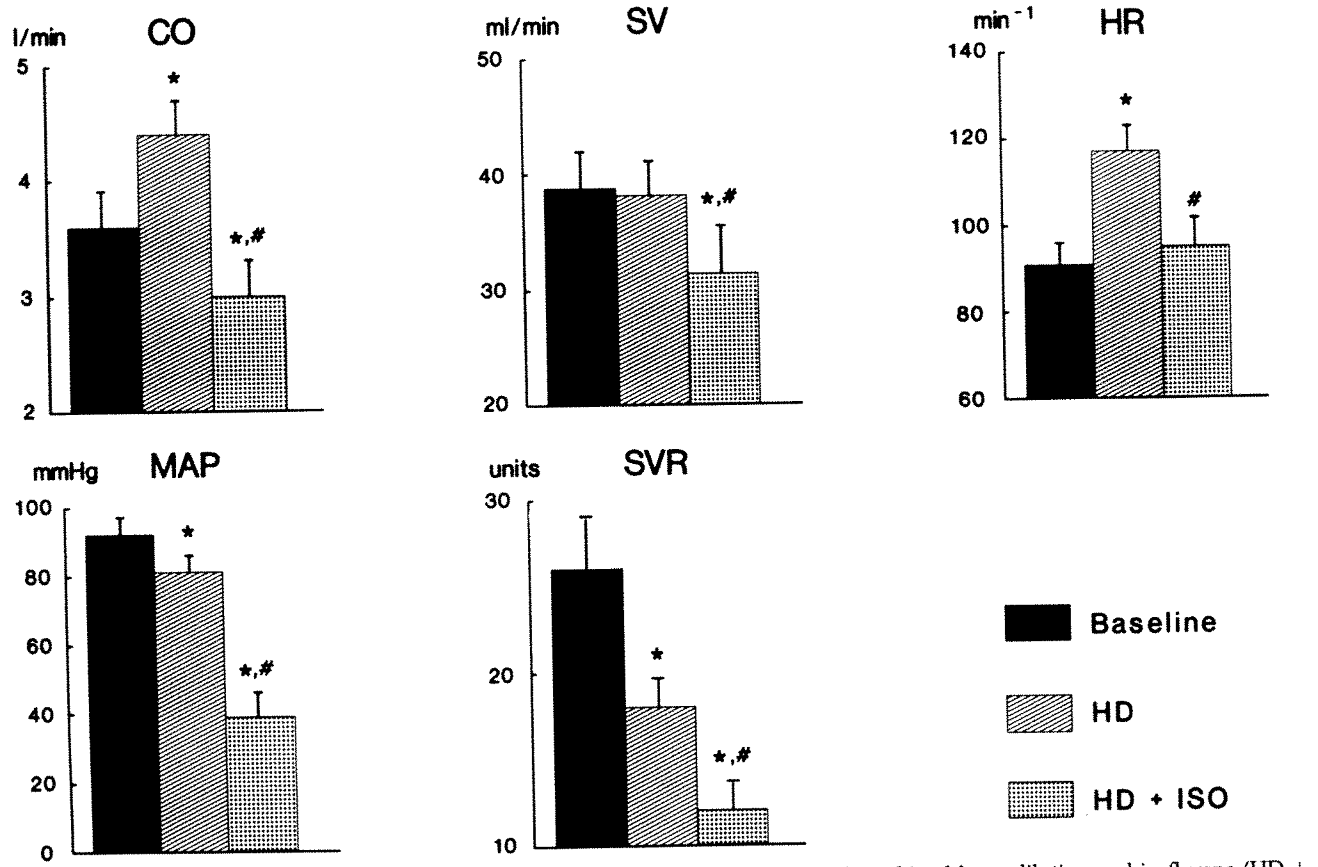

Figure 1. *Bars* represent mean values and SEM during baseline, hemodilution (HD), and combined hemodilution and isoflurane (HD + ISO). CO, cardiac output; SV, stroke volume; HR, heart rate; MAP, mean arterial blood pressure; SVR, systemic vascular resistance. $*P < 0.05$, compared with baseline. $\#P < 0.05$, compared with HD.

ring decreases in cardiac output (30%), stroke volume (15%), and heart rate (20%) (Figure 1).

Isoflurane-induced hypotension was associated with decreases in all splanchnic flows (Table 1). Compared with baseline values, the decreases in cardiac output and hepatic arterial blood flow were significant and of similar magnitude (Figure 2). Consequently, hepatic arterial blood flow decreased when expressed as a fraction of either total hepatic blood flow (from 17% ± 1% to 10% ± 1%) or cardiac output (from 3.5% ± 0.2% to 2.1% ± 0.2%). Although hepatic arterial and portal venous vascular resistances did not change significantly, there was a (further) decrease (55%) in superior mesenteric arterial vascular resistance (Table 1).

Systemic and Splanchnic O_2 Supply/Uptake Relationships

Normovolemic HD resulted in decreases in hepatic arterial, portal and hepatic venous (Figure 3), and mixed venous (Table 2) O_2 contents. This was due to both reduction in hematocrit and (except for arterial hemoglobin O_2 saturation, which remained unchanged) decreases in O_2 saturation. Consequently, except for hepatic arterial O_2 delivery, all O_2 delivery decreased (Table 2, Figure 3). Whole-body, liver, and small intestine O_2 uptake remained unchanged and were independent of O_2 delivery (Figure 4). All O_2 extraction ratios increased (Table 2).

Isoflurane-induced hypotension caused (further) decreases in portal and hepatic venous (Figure 3) and mixed venous (Table 2) O_2 contents owing to (further) reductions in the respective O_2 saturation. Because there was a uniform decrease in flows, all O_2 delivery decreased (Table 2, Figure 3).

Although systemic and small intestine O_2 extraction increased further, hepatic O_2 extraction did not change significantly (Table 2). Oxygen uptake of whole body and liver decreased, because the decrease in systemic and total hepatic O_2 delivery outweighed the respective increase in O_2 extraction, therefore becoming dependent on O_2 delivery (Figure 4). In contrast, small intestine O_2 uptake remained independent of O_2 delivery.

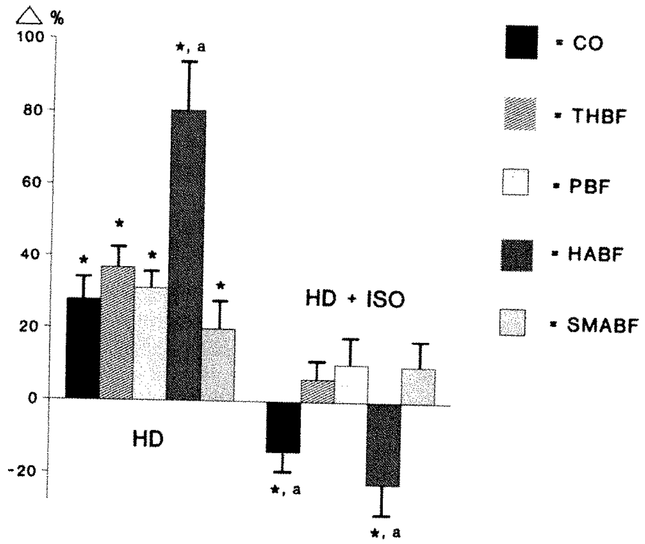

Figure 2. *Bars* represent percent changes (△) (mean and SEM) from baseline values during hemodilution (HD) and combined hemodilution and isoflurane (HD + ISO). CO, cardiac output; THBF, total hepatic blood flow; PBF, portal blood flow; HABF, hepatic arterial blood flow; SMABF, superior mesenteric arterial blood flow. $^*P < 0.05$, compared with no (zero) change. $^aP < 0.05$, compared with all other non *a*-marked flows.

Tissue Oxygenation of Liver and Small Intestine

Hemodilution resulted in decreases in mean liver and small intestine surface Po_2 values of approximately 35% and 20%, respectively (Table 2). In addition, the liver surface Po_2 histogram was broadened at the base and shifted to the left, with some Po_2 values in the hypoxic range (0–5 mm Hg) (Figure 5). In contrast, the small intestine surface Po_2 histogram retained its bell-shaped form, with no Po_2 values in the hypoxic range (Figure 6).

Isoflurane-induced hypotension caused a further 60% decrease in mean liver surface Po_2 (Table 2). In contrast, the 10% decrease in mean small intestine surface Po_2 was not significant. The liver surface Po_2 histogram was shifted even further to the left, with 38% of Po_2 values in the hypoxic range (0–5 mm Hg) (Figure 5). In contrast, the leftward shift of the small ntestine surface Po_2 histogram was minimal, with no Po_2 values <20 mm Hg (Figure 6).

epatic Metabolic Function

fter HD, hepatic lactate and pyruvate uptake renained unchanged (Table 2). Systemic arterial and ortal and hepatic venous pH values decreased (Tale 2).

Although hepatic pyruvate uptake continued to emain unchanged during superimposed isoflurane, lactate uptake decreased by 75% (Table 2). Portal and hepatic venous pH values decreased further.

Effects of Change in Experimental Sequence

In the four animals in which isoflurane was administered before HD, the changes between baseline on the one hand and combined isoflurane and HD on the other were quantitatively as well as qualitatively comparable to those observed during the reverse experimental sequence (Table 3). Mean percent changes of approximately 45 variables did not differ by >15% from those reported in the present study.

Effects of Time on Stability of Surgical Preparation During Maintained Hemodilution

In the three animals studied, changes in approximately 45 variables of hemodynamics, oxygenation, and metabolism did not exceed 15% over the 2-h period (Table 4).

Discussion

The principal findings of this study can be summarized as follows:

1. During severe HD (decrease in mean hematocrit from 29% to 15%), (a) cardiac output and splanchnic flows increased (with hepatic arterial blood flow increasing twice as much as all other flows); (b) hepatic arterial buffer response was not observed; (c) mean surface Po_2 of liver and small intestine decreased with a leftward shift of predominantly the hepatic surface Po_2 histogram; and (d) liver and small intestine O_2 uptake remained independent of O_2 delivery.
2. During superimposed isoflurane (1.45% end-tidal concentration), (a) mean arterial blood pressure, cardiac output, and splanchnic flows decreased; (b) a further decrease in mean hepatic surface Po_2 and a further (pronounced) leftward shift of the surface Po_2 histogram of the liver (38% of Po_2 values 0–5 mm Hg) were observed; and (c) hepatic O_2 uptake became O_2-delivery dependent.

These studies were conducted in anesthetized and ventilated pigs during laparotomy. The pig was chosen because of its anatomic and physiologic similarities to humans, particularly with respect to liver enzyme systems (9,14). Both laparotomy and mechanical ventilation are known to interfere with splanchnic perfusion (15,16). In contrast to barbiturates (15,17) and opiates (15,18), ketamine has no or little effect on liver and preportal circulation (19). The same is true for pancuronium (20). The effects of

Table 2. Variables for Systemic and Regional Oxygenation and Liver Function During Baseline, Hemodilution, and Combined Hemodilution and Isoflurane in Anesthetized Pigs

Variable	Baseline	HD	HD + Iso
Hemoglobin (g%)	9.1 ± 0.5	4.3 ± 0.2^{a}	4.1 ± 0.2^{a}
Hematocrit (%)	29 ± 1	15 ± 1^{a}	15 ± 1^{a}
Systemic oxygenation			
Pa_{O_2} (mm Hg)	109 ± 3	106 ± 6	110 ± 5
$P\bar{v}_{O_2}$ (mm Hg)	57 ± 2	49 ± 3^{a}	$38 \pm 2^{a,b}$
$S\bar{v}_{O_2}$ (%)	81 ± 2	71 ± 3^{a}	$55 \pm 4^{a,b}$
O_2 content, mixed venous (mL/100 mL)	9.4 ± 0.8	4.1 ± 0.4^{a}	$2.7 \pm 0.3^{a,b}$
O_2 delivery (mL/100 mL)	410 ± 28	256 ± 15^{a}	$147 \pm 14^{a,b}$
O_2 uptake (mL/min)	79 ± 9	79 ± 8	$67 \pm 4^{a,b}$
O_2 extraction (%)	18 ± 2	30 ± 4	$41 \pm 4^{a,b}$
Regional oxygenation			
Portal venous P_{O_2} (mm Hg)	55 ± 2	46 ± 1^{a}	$40 \pm 2^{a,b}$
Hepatic venous P_{O_2} (mm Hg)	40 ± 2	30 ± 3^{a}	$23 \pm 2^{a,b}$
Hepatic O_2 uptake (mL/min)	17 ± 2	19 ± 3	$11 \pm 2^{a,b}$
Hepatic O_2 extraction (%)	28 ± 5	41 ± 7^{a}	56 ± 8^{a}
Small intestine O_2 uptake (mL/min)	10 ± 1	9 ± 1	8 ± 1
Small intestine O_2 extraction (%)	22 ± 2	30 ± 4^{a}	$39 \pm 5^{a,b}$
Hepatic surface P_{O_2} (mm Hg)	56 ± 3	37 ± 4^{a}	$15 \pm 4^{a,b}$
Small intestine surface P_{O_2} (mm Hg)	54 ± 3	45 ± 2^{a}	39 ± 3^{a}
pH value			
Systemic arterial	7.36 ± 0.01	7.32 ± 0.02^{a}	7.31 ± 0.02^{a}
Portal venous	7.30 ± 0.01	7.26 ± 0.02^{a}	$7.22 \pm 0.02^{a,b}$
Hepatic venous	7.34 ± 0.01	7.30 ± 0.01^{a}	$7.23 \pm 0.02^{a,b}$
Hepatic uptake			
Pyruvate (μmol/min)	17 ± 4	21 ± 9	18 ± 10
Lactate (μmol/min)	477 ± 120	466 ± 123	$116 \pm 112^{a,b}$

HD, hemodilution; Iso, isoflurane; $P\bar{v}_{O_2}$, partial pressure in O_2, mixed venous blood; $S\bar{v}_{O_2}$, saturation of hemoglobin with O_2, mixed venous blood.
Values are mean ± SEM.
[a] $P < 0.05$, compared with baseline.
[b] $P < 0.05$, compared with HD.

flunitrazepam on the splanchnic circulation are unknown. It should therefore be realized that the effects associated with HD and isoflurane occurred during a baseline anesthesia with ketamine and flunitrazepam and during surgery. This, however, mimics the clinical situation in which patients receive baseline anesthesia during laparotomy, to which an inhaled anesthetic may subsequently be added to induce hypotension.

Six-percent hydroxyethyl starch was chosen as replacement fluid. It is a macromolecular polymer consisting of hydroxyethylated glucose molecules linked by α-1.4 bonds. The intravascular half-life is approximately 12 h. Owing to its physicochemical characteristics and minimal adverse effects, it is as suitable as 6% dextran 70 to induce HD (21).

If potentially adverse effects of acute HD are to be kept at a minimum, maintenance of normovolemia becomes essential. Although we did not determine actual blood volume, circumstantial evidence suggested that normovolemia was maintained. First, the amount of hydroxyethyl starch administered was slightly in excess of the amount of blood withdrawn. Second, right and left cardiac filling pressures remained unchanged throughout. Third, cardiac output could increase by 30%.

The concentration of 1.45% end-tidal isoflurane was chosen for two reasons. First, it had previously been used in the identical experimental model but without concomitant HD (8). Using the same concentration again enabled us to assess the modifying effects of underlying HD on subsequent isoflurane administration. Under conditions of preexisting HD, 1.45% isoflurane caused pronounced hypotension. It thus needs to be emphasized that animals with a presumably normal circulation were studied. Translation of this data to patients with diseased circulation (e.g., long-standing hypertension or atherosclerosis) is therefore unwarranted.

Second, the concentration of 1.45% isoflurane corresponds to 1 MAC in pigs (7). On the basis of recently revised MAC values for isoflurane in pigs (2.04%) (22), it is possible that the end-tidal concentration used in this study may be somewhat <1 MAC.

The transparenchymatous cannulation of the left hepatic vein was performed as previously described (8,23). Correct position of the catheter tip in the

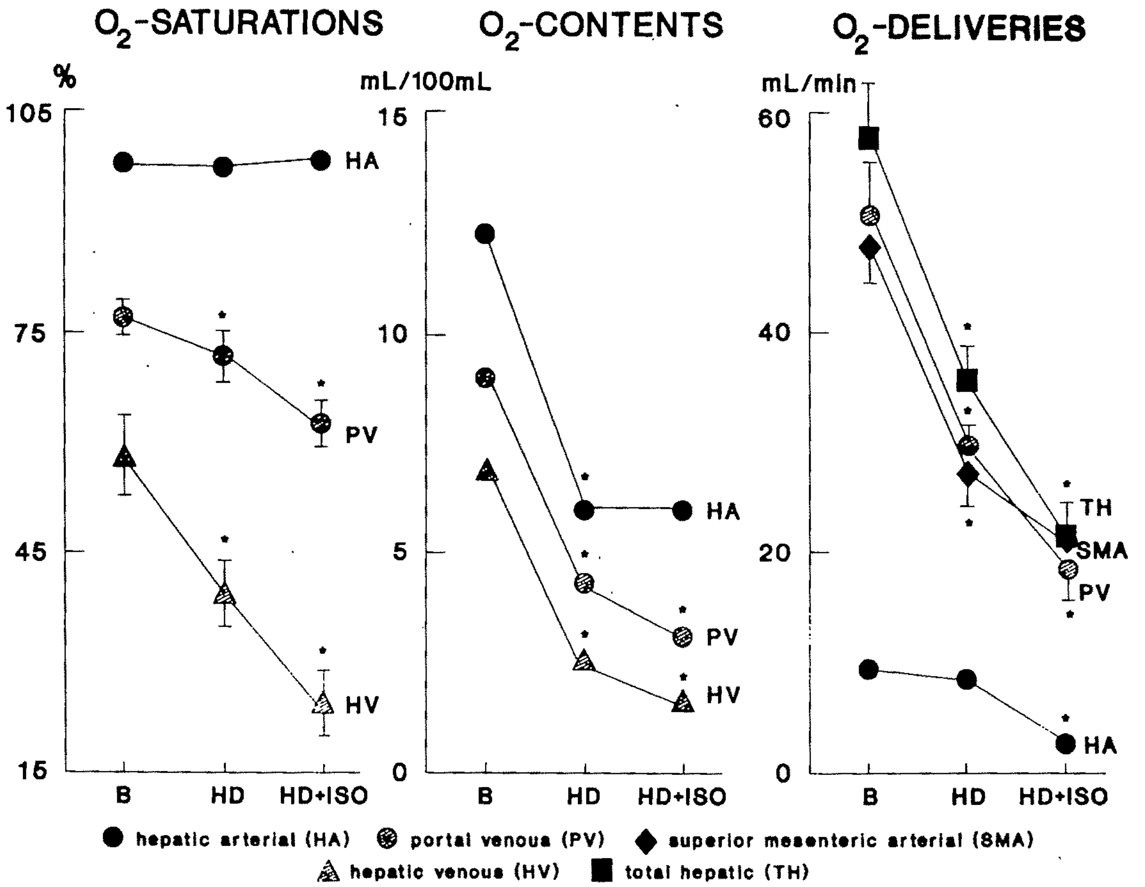

Figure 3. Hemoglobin O_2 saturation, contents, and delivery during baseline (B), hemodilution (HD), and combined hemodilution and isoflurane (HD + ISO). Symbols represent mean values and SEM. (SEM is absent when value is ≤1.) $^*P < 0.05$, compared with preceding value.

region where the four hepatic veins merge was verified at autopsy. This technique allows collection of mixed venous hepatic blood while avoiding the ventilation-related changes in catheter position and partial occlusion of hepatic venous outflow sometimes associated with hepatic vein catheterization via internal jugular vein (23).

The portal vein was catheterized using Seldinger's technique. Preliminary studies had shown identical portal venous flows before and after portal vein catheterization, thus excluding vascular obstruction by the catheter.

The technique of measuring surface Po_2 using O_2-sensitive multiwire surface electrodes has been well established (10,11). This technique allows determination of tissue Po_2 without causing tissue trauma or interference with the microcirculation (11). However, that liver surface Po_2 values are not entirely representative of whole-organ oxygenation cannot entirely be ruled out. Owing to species-related distributions of hepatic arterial and portal blood flow, surface Po_2 values may reflect primarily hepatic arterial blood flow (24). In addition, in pigs the liver capsule contains a dense arterial network (25). Relatively high mean surface Po_2 values and a rightward localization of the Po_2 histograms during baseline conditions would support such possibilities. Al-

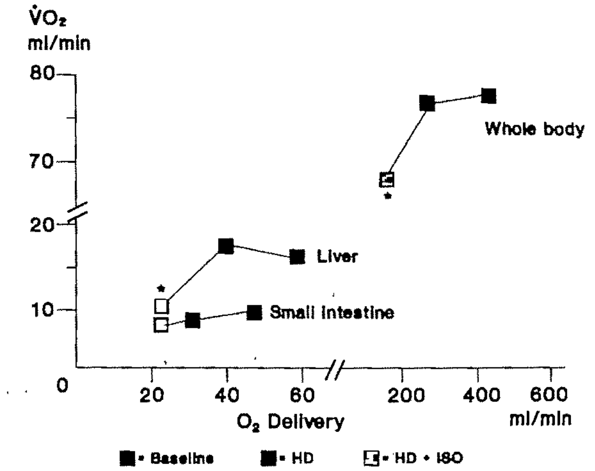

Figure 4. Relationship between O_2 uptake ($\dot{V}O_2$) and O_2 delivery of whole body, liver, and small intestine during baseline, hemodilution (HD), and combined hemodilution and isoflurane (HD + ISO). For reasons of clarity, only mean values are depicted (see Table 2 for SEM). $^*P < 0.05$, compared with both preceding values.

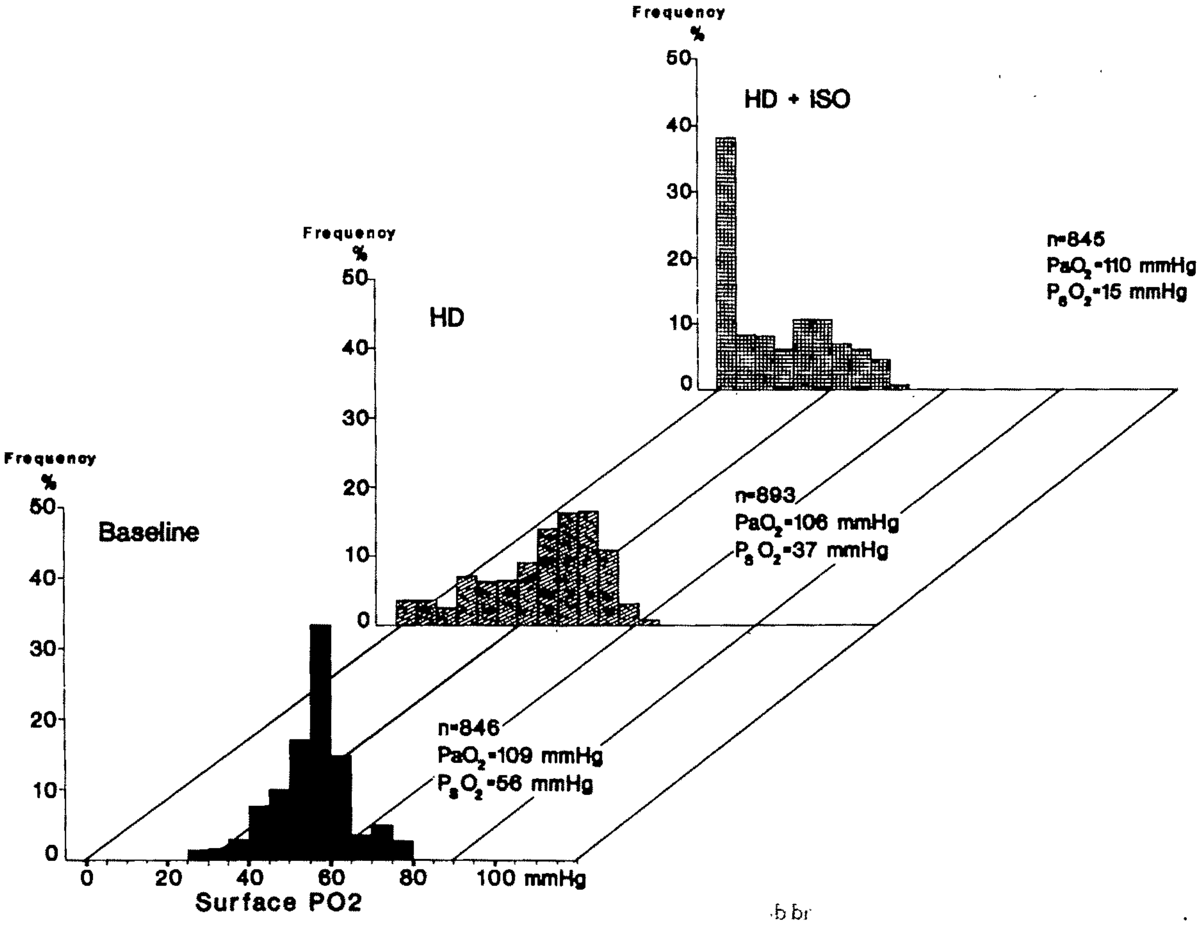

Figure 5. Summary histogram of liver surface Po_2 during baseline, hemodilution (HD), and combined hemodilution and isoflurane (HD + ISO). n, total number of measurements; Pso_2, mean surface tissue Po_2; Pao_2, mean arterial Po_2 during recording of histograms.

though polarographic reduction of halothane at the Po_2 electrode yields artificially elevated Po_2 values (26), isoflurane does not interfere with this technique (11).

The protocol required baseline anesthesia and extensive surgical preparation. In addition, isoflurane was always administered after established HD. These factors may have influenced the results. However, the data obtained in three animals with 2 h of maintained HD and in those four with a reverse sequence of interventions (i.e., HD after isoflurane) would rule out significant spontaneous deterioration of the preparation or major modification of the results by the experimental sequence.

In agreement with previous work (27–30), HD caused an increase in cardiac output. In contrast to previous findings, this increase was due to an increase in heart rate rather than in stroke volume. This response in heart rate is likely to vary with baseline heart rate. Heart rate is unlikely to increase (even further) if it is markedly elevated during baseline conditions (31). If hypovolemia would have been the reason for the development of tachycardia, stroke volume would have decreased, cardiac output would not have increased by 30%, and cardiac filling pressures would not have remained unchanged. In agreement with previous work (28,29), there was a marked reduction in systemic vascular resistance and a small (10%) but significant decrease in mean arterial pressure.

Compared with HD alone, addition of approximately 1 MAC isoflurane caused a pronounced decrease in cardiac output to values below baseline related to decreases in stroke volume and heart rate. The decrease in stroke volume despite unchanged indices of preload (right and left cardiac filling pressures) and lowered indices of afterload (mean arterial pressure, systemic vascular resistance) reflects the well-known negative inotropic properties of isoflurane (32,33).

The cardiovascular depression elicited by isoflurane during underlying severe HD was more pronounced than previously observed in the identical experimental model but without preexisting HD (8).

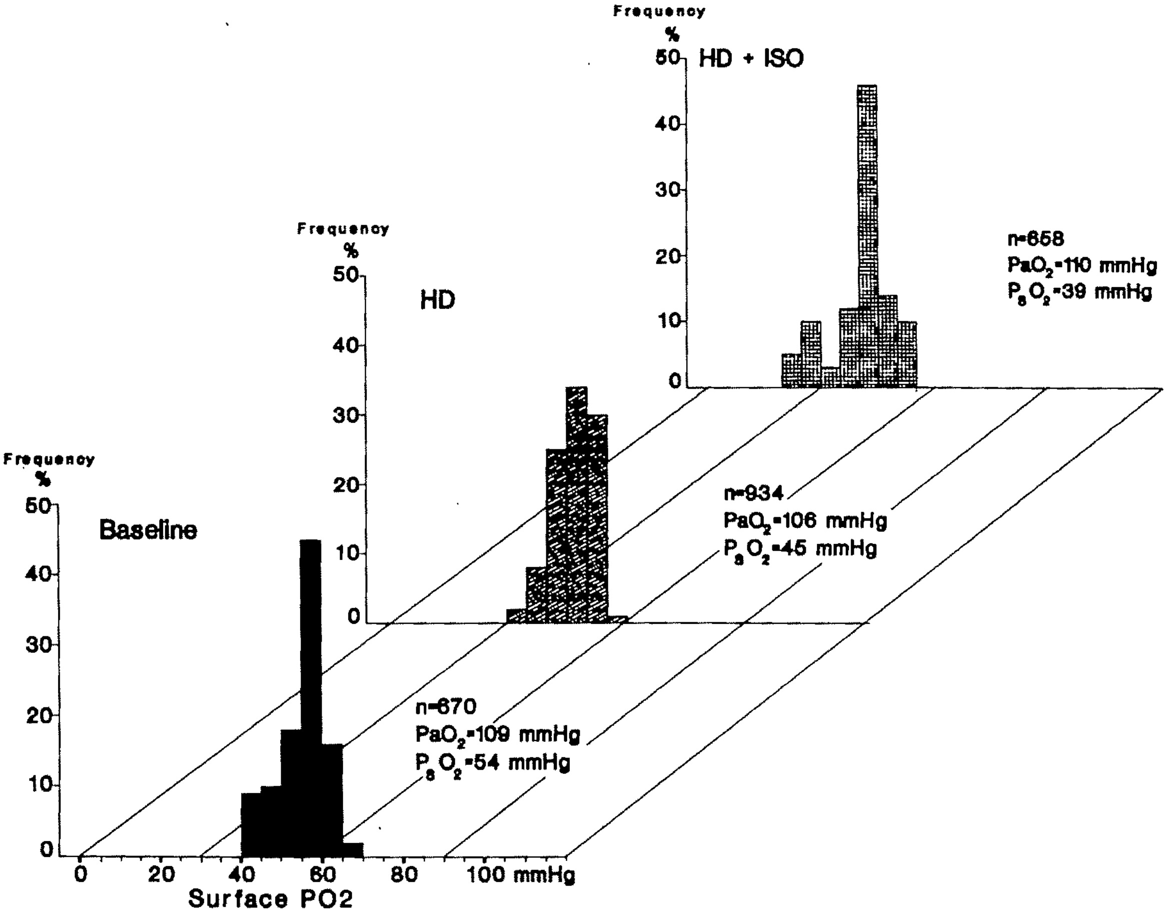

Figure 6. Summary histograms of small intestinal surface Po_2 during baseline, hemodilution (HD), and combined hemodilution and isoflurane (HD + ISO). Abbreviations as in Figure 5.

Specifically, the decrease in mean arterial pressure was significantly greater (50% vs 30%). It is conceivable that this was in part related to both the difference in underlying vascular motor tone and reactivity associated with the decrease in viscosity and the decrease in myocardial contractility as a consequence of inadequate oxygen transport to the myocardium during HD and isoflurane. Hemodilution had already caused a 30% reduction in systemic vascular resistance, which, however, was compensated by increases in heart rate and cardiac output. When these compensatory mechanisms were eliminated by isoflurane, the further 25% reduction in systemic vascular resistance now provoked an unopposed decrease in perfusion pressure. Cardiovascular depression is also reflected by the decrease in arterial pH.

There are few data on the effects of induced hypotension during HD available for direct comparison. During nitroprusside-induced (30) or adenosine-induced (29) hypotension, cardiac output decreased when compared with HD alone, but it either remained unchanged (30) or was even elevated (29) when compared with baseline status. Differences in results can easily be explained on the basis of differences in species (pigs vs dogs), baseline anesthesia (flunitrazepam/ketamine vs halothane and pentobarbital), degree of HD (hematocrit values of 14% vs 22%), baseline heart rates (90 vs 130–160 beats/min), and drugs used to induce hypotension (combined cardiodepressant and vasodilator vs pure vasodilators).

Hemodilution caused all splanchnic flows to increase proportionally with cardiac output, except for hepatic arterial blood flow, which increased twice as much (Figure 2). This finding would suggest active dilation of the hepatic vascular bed in addition to increases in flow related to changes in cardiac output and viscosity. It can only be speculated that the decreases in hepatic venous Po_2, O_2 saturation, and pH provided additional stimuli for active hepatic arterial vasodilation to compensate for the decrease in O_2 delivery.

Although such reasoning might seem intuitively obvious, the hepatic arterial buffer response (34) would predict a decrease in hepatic arterial blood flow in response to an increase in portal blood flow

Table 3. Systemic and Regional Hemodynamics and Oxygenation and Liver Function During Baseline and After Hemodilution During 1 MAC Isoflurane Anesthesia in Four Anesthetized Pigs

Variable	Baseline	Iso + HD[a]
Heart rate (beats/min)	102 ± 15	114 ± 15
Cardiac output (L/min)	9.3 ± 0.1	4.4 ± 0.4
Stroke volume (mL)	41 ± 4	29 ± 3
Intravascular pressure (mm Hg)		
Mean arterial	83 ± 9	48 ± 11
Central venous	2.2 ± 0.2	2.4 ± 0.2
Pulmonary capillary wedge	8.0 ± 2.3	8.2 ± 1.8
Portal venous	7.0 ± 0.8	6.5 ± 0.6
Hepatic venous	2.2 ± 0.2	2.4 ± 0.2
Blood flow (mL/min)		
Total hepatic	704 ± 76	678 ± 40
Portal venous	627 ± 67	620 ± 40
Hepatic arterial	77 ± 9	58 ± 3
Superior mesenteric arterial	449 ± 56	423 ± 73
Vascular resistance (U)		
Systemic	23 ± 7	14 ± 3
Portal venous	8 ± 1	7 ± 1
Hepatic arterial	1123 ± 275	794 ± 41
Superior mesenteric arterial	183 ± 45	105 ± 14
Hemoglobin (g%)	9.3 ± 0.1	4.4 ± 0.4
Hematocrit (%)	29 ± 1	14 ± 1
O_2 pressure (mm Hg)		
Arterial	102 ± 7	109 ± 9
Mixed venous	52 ± 3	35 ± 4
Portal venous	50 ± 2	31 ± 3
Hepatic venous	38 ± 2	21 ± 3
O_2 saturation (%)		
Arterial	98 ± 1	98 ± 1
Mixed venous	79 ± 3	45 ± 5
Portal venous	76 ± 3	54 ± 7
Hepatic venous	48 ± 3	24 ± 2
O_2 content (mL/100 mL)		
Arterial	12.5 ± 0.3	6.1 ± 0.4
Mixed venous	9.9 ± 0.5	2.7 ± 0.8
Portal venous	9.6 ± 0.8	3.4 ± 0.9
Hepatic venous	6.1 ± 0.4	1.5 ± 0.3
O_2 delivery (mL/min)		
Systemic	521 ± 85	208 ± 35
Total hepatic	71 ± 11	24 ± 6
Portal venous	61 ± 10	20 ± 5
Hepatic arterial	10 ± 1	4 ± 1
Superior mesenteric arterial	56 ± 7	25 ± 2
O_2 uptake (mL/min)		
Whole body	114 ± 24	89 ± 21
Liver	28 ± 4	14 ± 5
Small intestine	12 ± 2	10 ± 3
O_2 extraction (%)		
Systemic	21 ± 4	55 ± 4
Liver	39 ± 2	54 ± 9
Small intestine	23 ± 6	42 ± 13
Surface O_2 pressure		
Liver	58 ± 3	21 ± 5
Small intestine	53 ± 7	20 ± 8
Hepatic uptake (μmol/min)		
Lactate	528 ± 89	154 ± 127
Pyruvate	24 ± 5	19 ± 7
pH value		
Systemic arterial	7.38 ± 0.01	7.31 ± 0.02
Portal venous	7.29 ± 0.01	7.23 ± 0.02
Hepatic venous	7.33 ± 0.01	7.21 ± 0.02

HD, hemodilution; Iso, isoflurane.

Values are mean ± SEM.

[a] In contrast to the original protocol, the values listed under Iso + HD were obtained after hemodilution had been superimposed on underlying isoflurane anesthesia (rather than superimposing isoflurane on underlying hemodilution). Changes from baseline are quantitatively similar to those listed in Tables 1 and 2 as HD + Iso.

Table 4. Effect of Time on Systemic and Regional Hemodynamics and on Oxygenation and Liver Function During Hemodilution in Three Anesthetized Pigs

Variable	HD t_0	HD t_{2h}
Heart rate (beats/min)	120 ± 21	126 ± 30
Cardiac output (L/min)	4.0 ± 0.7	3.9 ± 0.4
Stroke volume (mL)	33 ± 7	31 ± 8
Intravascular pressure (mm Hg)		
Mean arterial	94 ± 3	88 ± 14
Central venous	2.1 ± 0.4	2.0 ± 0.3
Pulmonary capillary wedge	7.9 ± 1.0	8.2 ± 1.2
Portal venous	7.2 ± 1.1	7.5 ± 0.5
Hepatic venous	2.8 ± 0.5	2.9 ± 0.8
Blood flow (mL/min)		
Total hepatic	848 ± 24	921 ± 18
Portal venous	707 ± 13	747 ± 43
Hepatic arterial	177 ± 31	175 ± 25
Superior mesenteric arterial	561 ± 15	592 ± 26
Vascular resistance (U)		
Systemic	24 ± 5	23 ± 9
Portal venous	7 ± 2	7 ± 2
Hepatic arterial	536 ± 108	493 ± 148
Superior mesenteric arterial	124 ± 24	129 ± 19
Hemoglobin (g%)	4.4 ± 0.3	4.1 ± 0.2
Hematocrit (%)	15 ± 1	15 ± 1
O_2 pressure (mm Hg)		
Arterial	107 ± 3	108 ± 2
Mixed venous	47 ± 3	46 ± 2
Portal venous	45 ± 2	43 ± 3
Hepatic venous	29 ± 3	28 ± 3
O_2 saturation (%)		
Arterial	98 ± 1	99 ± 1
Mixed venous	58 ± 1	55 ± 3
Portal venous	53 ± 4	52 ± 5
Hepatic venous	45 ± 9	43 ± 9
O_2 content (mL/100 mL)		
Arterial	5.4 ± 0.8	5.8 ± 0.8
Mixed venous	3.1 ± 0.2	3.1 ± 0.2
Portal venous	2.9 ± 0.2	3.2 ± 0.1
Hepatic venous	2.5 ± 0.6	2.8 ± 0.5
O_2 delivery (mL/min)		
Systemic	217 ± 53	224 ± 58
Total hepatic	35 ± 2	36 ± 1
Portal venous	25 ± 1	26 ± 2
Hepatic arterial	10 ± 3	10 ± 3
Superior mesenteric arterial	35 ± 2	34 ± 1
O_2 uptake (mL/min)		
Whole body	92 ± 25	104 ± 31
Liver	18 ± 4	19 ± 4
Small intestine	10 ± 2	11 ± 1
O_2 extraction (%)		
Systemic	42 ± 1	46 ± 2
Liver	47 ± 16	52 ± 12
Small intestine	37 ± 4	39 ± 4
Surface O_2 pressure (mm Hg)		
Liver	48 ± 3	49 ± 4
Small intestine	44 ± 6	43 ± 7
Hepatic uptake (μmol/min)		
Lactate	523 ± 87	495 ± 157
Pyruvate	27 ± 8	22 ± 10
pH value		
Systemic arterial	7.36 ± 0.02	7.35 ± 0.02
Portal venous	7.27 ± 0.02	7.26 ± 0.02
Hepatic venous	7.30 ± 0.01	7.29 ± 0.02

t_0, measurements during hemodilution (HD) after stabilization; t_{2h}, measurements 2 h later (without further intervention).
Values are mean ± SEM.

(as observed during HD). This buffer response suggests that total hepatic perfusion is flow regulated rather than demand dependent. It is postulated that the rate of intrahepatic adenosine washout forms the basis for the hepatic arterial buffer response (35).

Our findings either provide evidence against the adenosine-washout hypothesis (i.e., total hepatic perfusion is not simply flow regulated), or they indicate that factors associated with HD overcome or at least modulate the hepatic arterial buffer response. Such factors may be related to changes in cardiac output, blood viscosity, hepatic oxygenation, or hepatic venous pH. However, this does not explain entirely why hepatic arterial vascular resistance declined almost twice as much as did the resistances of other vascular beds. It is conceivable that the hepatic arterial buffer response is not as effective in pigs as it is in cats (35) or dogs (36). It also is possible that the degree of the response varies with the baseline anesthesia and with the initial value for the relative contribution of hepatic arterial blood flow to total hepatic blood flow.

Most previous studies found insignificant changes in hepatic arterial blood flow in response to HD (27,29,37,38). Only one study (39) in addition to ours, showed a significant increase in hepatic arterial blood flow. Total hepatic blood flow was found to be unchanged (37) or to increase (39); portal blood flow also was found to increase (37).

Direct comparison of these results with ours is difficult because of differences in species (pigs vs cats vs dogs vs rats), in baseline anesthesia (ketamine/flunitrazepam vs pentobarbital vs neuroleptic vs conscious), in degree of HD, in means of achieving HD, and in methods of determining hepatic blood flow (electromagnetic flow probes vs microspheres vs bromsulphalein vs reservoir). Furthermore, in most of these studies, portal blood flow was not determined (27,29,38,39). Such lack of flow measurement will render determination of total hepatic blood flow and, consequently, any evaluation of a potential hepatic arterial buffer response impossible.

Isoflurane-induced hypotension was associated with decreases in all splanchnic flows (Figure 2). There were, however, quantitative differences among flows. Although superior mesenteric arterial, portal venous, and total hepatic blood flow returned to baseline values, hepatic arterial blood flow decreased to below (≈25%) baseline. Of note, unlike during HD, the change in hepatic arterial blood flow was now proportional to that of cardiac output. Further decreases in systemic and superior mesenteric arterial vascular resistances but not in hepatic arterial vascular resistance in response to administration of isoflurane would suggest that HD had resulted in near maximal vasodilation of only the hepatic arterial vascular bed, with flow now becoming pressure dependent. In this case, hepatic arterial blood flow would be expected to decrease in parallel with the reduction in perfusion pressure. Apparently, further decreases in portal and hepatic venous Po_2 saturation and in pH did not provide (potent enough?) stimuli for additional vasodilation.

These findings are in marked contrast to those previously observed in the identical experimental model but without preexisting HD (8). The same concentration of isoflurane had resulted in a 40% increase in hepatic arterial blood flow on the one hand and in a 15%–25% decrease in portal, superior mesenteric arterial, and total hepatic blood flow on the other. The increase in hepatic arterial blood flow (in contrast to the decrease observed in the present study) might be explained on the basis of either preserved hepatic arterial buffer response (i.e., increase in hepatic arterial blood flow in response to the decrease in portal blood flow), selective isoflurane-induced vasodilation of the hepatic arterial vascular bed (not previously dilated by HD), or by a less pronounced reduction in systemic arterial pressure (mean arterial pressure of 65 vs 40 mm Hg). On the other hand, it is difficult to explain why, in the present study, splanchnic flows were maintained (compared with baseline values) rather than decreased (as in the previous study) despite a profound decrease in perfusion pressure. It can only be postulated that the underlying HD modified (by mechanisms unidentified by this study) vascular reactivity.

In other studies of nonhemodiluted animals, isoflurane caused decreases in total hepatic and portal blood flows (15,40) and an increase in hepatic arterial blood flow in nonlaparotomized animals (7,41,42) but not in laparotomized miniature pigs (43).

Owing to decreases in hematocrit and O_2 saturation (portal and hepatic venous), O_2 contents of all vascular beds decreased (Figure 3). Because these decreases in O_2 content mostly outweighed the increases in flows, O_2 delivery decreased (except for hepatic arterial). Because of its unchanged O_2 saturation and the disproportional increase in flow, the hepatic artery was the only vascular bed that maintained O_2 delivery. In this model, hepatic arterial blood flow contributes just between 12% (baseline) and 17% (HD) to total hepatic blood flow; therefore, unchanged hepatic arterial O_2 delivery could not compensate for the marked decrease in portal venous O_2 delivery (as reflected by the decrease in total hepatic O_2 delivery). The pig compensated for reduced O_2 contents by progressively increasing flows (by lowering vascular resistances) and O_2 extraction ratios.

Both portal and hepatic venous pH values and hepatic and small intestine surface Po_2 decreased. In addition, the summary Po_2 histogram of the liver broadened at the base and shifted leftward, with 20% of Po_2 values <20 mm Hg. This is suggestive evidence of disturbed microcirculation. Although a tendency for a leftward shift also was observed in the surface Po_2 histogram of the small intestine, these changes were less pronounced: no Po_2 values were <25 mm Hg. Combined evidence thus suggests that during severe HD, compensatory mechanisms (i.e., increases in flows and O_2 extraction ratios) were no longer able to fully compensate for the decreases in O_2 delivery.

Despite decreases in O_2 delivery between 30% and 40%, O_2 uptake of liver and small intestine did not decrease significantly. This implies that the point at which tissue O_2 uptake becomes limited by delivery in a supply-dependent manner (i.e., critical O_2 delivery) had not yet been reached.

During superimposed isoflurane-induced hypotension, portal and hepatic venous O_2 content decreased even further, related to decreases in the respective O_2 saturation. In contrast, hepatic arterial O_2 content was maintained, owing to unchanged O_2 saturation. Because there was a uniform decrease in flow, all O_2 delivery decreased.

There were also further decreases in portal and hepatic venous pH and in hepatic surface Po_2. The leftward shift of the summary Po_2 histogram became pronounced, with 80% of Po_2 values <20 mm Hg and with almost 40% of Po_2 values in the hypoxic range (i.e., 0–5 mm Hg). All factors taken together, this would suggest severely impaired hepatic microcirculation. This would correlate with evidence of impaired hepatic function, as suggested by the decrease in hepatic lactate uptake.

As with HD alone, the effects on the surface Po_2 of the small intestine were less pronounced. The 10% decrease in mean surface Po_2 was statistically not significant, and the leftward shift of the summary histogram was relatively small, with no Po_2 values <20 mm Hg. Two findings might help to explain why the small intestinal microcirculation was apparently somewhat less disturbed than the hepatic circulation. First, the decrease in superior mesenteric arterial O_2 delivery was relatively less than that in total hepatic delivery (20% vs 35% compared with HD alone). Second, whereas hepatic O_2 extraction did not increase further, there was an additional increase in small intestinal O_2 extraction.

Overall evidence clearly suggests that during combined HD and isoflurane-induced hypotension, adaptive mechanisms (i.e., increases in flows and O_2 extraction) are almost completely exhausted and no longer compensate for decreases in O_2 content to maintain tissue oxygenation. In accordance with these findings, O_2 uptake of liver (and of whole body) decreased (Figure 4). Thus, the point of critical O_2 delivery had been reached. In contrast, small intestinal O_2 uptake remained supply independent.

Data for direct comparison are limited. When isoflurane was administered at the same concentration in the identical experimental model but without underlying HD, there were also decreases in O_2 delivery to liver and small intestine, in hepatic and small intestine surface Po_2, and a leftward shift of the surface summary Po_2 histograms (8). However, in contrast to the present findings, extraction ratios of liver and small intestine, portal and hepatic venous O_2 contents, and hepatic O_2 and lactate uptake remained unchanged. In addition, despite the leftward shift of the surface Po_2 histograms, hypoxic Po_2 values (0–5 mm Hg) were not observed. This would suggest that in the absence of HD, the increases in O_2 extraction sufficiently compensated for the decreases in O_2 delivery. Other investigators have made similar observations (37). In contrast, and in agreement with species-related differences in liver blood flow distribution, in a dog model, hypoxic (0–5 mm Hg) surface Po_2 values were observed in 8% of all Po_2 measurements during piritramid baseline anesthesia and in 20% of all measurements during 1 MAC isoflurane (11).

In conclusion, we have shown that in anesthetized and laparotomized pigs, even severe, acute normovolemic HD (from an initial hematocrit of 29% down to 14%) with 6% hydroxyethyl starch does not necessarily have grossly adverse effects on liver and small intestine (as suggested by statistically insignificant changes in splanchnic O_2 and hepatic lactate uptake). However, decreases in mean surface Po_2 of liver and small intestine, broadening and leftward shift of the liver surface Po_2 histogram, and decreases in portal and hepatic venous pH and O_2 content values provide evidence that compensatory mechanisms were becoming exhausted.

When isoflurane-induced hypotension was superimposed on HD, splanchnic hemodynamics and oxygenation became severely impaired (as suggested by decreases in hepatic O_2 and lactate uptake, a marked reduction in mean liver surface Po_2, and a pronounced leftward shift of the liver surface Po_2 histogram). This clearly indicates that mechanisms usually compensating for decreases in O_2 content (i.e., decreases in vascular resistance, increases in flows and O_2 extraction) were no longer effective. It is conceivable that the cardiodepressant effect of isoflurane accentuated the potentially adverse effects of combined reductions in O_2 content and perfusion pressure on regional perfusion and oxygenation. These data would thus suggest that combined HD and deliberate hypotension should be used with extreme caution in patients, especially when a mixed cardiodepressant and vasodilator (e.g., isoflurane) drug is chosen for inducing hypotension during underlying normovolemic anemia.

It remains to be determined whether the human splanchnic circulation responds to acute HD in a manner similar to that of the pig. Normal hematocrit values in humans are approximately 45% (rather than 30% as in the pig). We are therefore unable to define the human correlate to a hematocrit of 15% in the pig. In the human, comparably low values may reflect a much greater degree of HD. If only the percent changes in hematocrit after HD (50%) were applied, this would correspond to absolute hematocrit values of approximately 20% in humans.

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Appendix: Formulas Applied

Vascular Resistance

$$\text{SVR (U)} = \frac{\text{MAP (mm Hg)} - \text{CVP (mm Hg)}}{\text{CO (L/min)}},$$

$$\text{HAVR (U)} = \frac{\text{MAP (mm Hg)} - \text{HVP (mm Hg)}}{\text{HABF (mL/min)}} \times 10^3,$$

$$\text{PVVR (U)} = \frac{\text{PVP (mm Hg)} - \text{HVP (mm Hg)}}{\text{PBF (mL/min)}} \times 10^3,$$

$$\text{SMAVR (U)} = \frac{\text{MAP (mm Hg)} - \text{PVP (mm Hg)}}{\text{SMABF (mL/min)}} \times 10^3,$$

where SVR, HAVR, PVVR, and SMAVR are systemic, hepatic arterial, portal venous, and superior mesenteric arterial vascular resistances, respectively; MAP, CVP, PVP, and HVP are mean arterial, central venous, portal venous, and hepatic venous pressures, respectively; CO is cardiac output; HABF, PBF, and SMABF are hepatic arterial, portal venous, and superior mesenteric arterial blood flows.

Oxygen Supply/Uptake

$$O_2 \text{ content} = \text{Hb} \times O_2 \text{ saturation} \times 1.34 + P_{O_2} \times 0.0031,$$

$$O_2 \text{ delivery} = O_2 \text{ content} \times \text{flow},$$

$$DO_2TH = DO_2HA + DO_2PV,$$

$$DO_2HA = CO_2A \times HABF \times 10^{-2},$$

$$DO_2PV = CO_2PV \times PVF \times 10^{-2},$$

$$DO_2SMA = CO_2A \times SMABF \times 10^{-2},$$

$$VO_2TH = (CO_2PV - CO_2HV) \times PBF \times 10^{-2} + (CO_2A - CO_2HV) \times HABF \times 10^{-2},$$

$$VO_2SI = (CO_2A - CO_2PV) \times SMABF \times 10^{-2},$$

$$EO_2TH = VO_2TH/DO_2TH,$$

$$EO_2SI = VO_2SI/DO_2SMA,$$

where DO_2TH, DO_2HA, DO_2PV, and DO_2SMA are total hepatic, hepatic arterial, portal venous, and superior mesenteric arterial O_2 deliveries; CO_2A, CO_2PV, and CO_2HV are systemic arterial, portal venous, and hepatic venous O_2 contents; VO_2TH and VO_2SI are total hepatic and small intestinal O_2 uptake; EO_2TH and EO_2SI are total hepatic and small intestinal O_2 extraction ratios.

Hepatic Metabolism

$$\text{Hepatic lactate uptake} = (\text{CLACPV} - \text{CLACHV}) \times \text{PBF} + (\text{CLACHA} - \text{CLACHV}) \times \text{HABF},$$

$$\text{Hepatic pyruvate uptake} = (\text{CPYRPV} - \text{CPYRHV}) \times \text{PBF} + (\text{CPYRHA} - \text{CPYRHV}) \times \text{HABF},$$

where CLAC and CPYR are lactate and pyruvate concentrations in hepatic arterial (HA), portal venous (PV), and hepatic venous (HV) blood.

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Greater Neuromuscular Blocking Potency of Atracurium During Hypothermic Than During Normothermic Cardiopulmonary Bypass

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Previous studies drew attention to the greater neuromuscular blocking potency of atracurium during, than before or after, hypothermic cardiopulmonary bypass (CPB) while disregarding the periods of normothermic perfusion. We recorded the evoked twitch tension in 15 patients during nitrous oxide/narcotic anesthesia who were undergoing open heart surgery. Atracurium was injected as an initial bolus dose of 460 μg/kg. Waning neuromuscular blockade was enhanced by repeat injections of 138 μg/kg whenever the twitch tension attained 25% of control. During hypothermic (<32°C) and normothermic (>34°C) CPB, the times of onset of the maintenance doses were 57% and 18% longer, respectively, than before CPB ($P < 0.05$). Maintenance doses of atracurium were required every 24 ± 4 min (mean ± SD) before CPB, every 45 ± 8 min ($P < 0.05$) during hypothermia, every 22 ± 3 min during normothermic perfusion, and every 23 ± 3 min after CPB. In conclusion, the patients' changing demand of atracurium paralleled the changes of temperature rather than the institution and cessation of CPB.

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Hypothermic cardiopulmonary bypass (CPB) causes a 35% reduction in the rate of atracurium infusion necessary to maintain a 95% neuromuscular blockade (1,2). In one study, an average of 80% of the prebypass rate of infusion had to be resumed after cessation of CPB (1). In the other study, after the end of CPB, the time from the end of infusion to recovery to 95% of control neuromuscular transmission averaged 85 min (2) (i.e., approximately three times as long as in continuously normothermic patients [3]). Because both studies (1,2) disregarded the period of normothermic perfusion, the present study was designed to quantitate the impact of normothermic versus hypothermic CPB on atracurium-induced neuromuscular blockade.

Methods

After approval of the study by the hospital ethical committee, 15 adult patients, ASA physical status III and IV, undergoing open heart surgery gave their informed consent to participate in the study. Patients with neuromuscular, kidney, or liver disease and those taking medication known to interact with muscle relaxants were excluded from the study. All patients were premedicated with flunitrazepam (2 mg) administered orally 90 min before the induction of anesthesia. Anesthesia was induced with midazolam (10–15 mg IV) and fentanyl (0.75–1.5 mg IV). After losing consciousness, the patients received 100% oxygen via face mask over 10 min. Anesthesia was maintained with an infusion of fentanyl (0.8–1.2 mg/h) and midazolam (10–15 mg/h) during mechanical ventilation with 50% oxygen in air, adjusted for 35–45 mm Hg end-tidal carbon dioxide concentration. The pump was primed with lactated Ringer's solution (2200 mL) including heparin (2000 U) and aprotinin (2×10^{-6} U). Capillary oxygenators were used. The pump flow was 2.4 L/m^2. Neuromuscular transmission was monitored by the evoked twitch tension (boomerang force displacement transducer [4]) in response to supramaximal train-of-four stimuli (2 Hz/2 s every 15 s) administered to the ulnar nerve at the wrist via surface electrodes. Neuromuscular monitoring was instituted after the loss of consciousness, and the recording system was allowed to stabilize for 10 min until a bolus dose of atracurium (460 μg/kg, equal to twice the effective dose for 95% depression of twitch tension) was injected intrave-

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nously over 60 s. The trachea was intubated when the twitch response was completely abolished. Waning neuromuscular blockade was enhanced by intravenous injection of constant maintenance doses of atracurium (138 μg/kg, equal to 0.6 times the effective dose for 95% depression of twitch tension) whenever the first twitch response of a train-of-four (T1) had attained 25% of its control. Spontaneous recovery of neuromuscular transmission to at least 75% of control twitch tension was allowed to occur after the last maintenance dose of atracurium. The twitch recordings were evaluated for the following variables: time from end of injection of the initial dose to recovery of 25% of control twitch tension; time from end of injection of the maintenance doses to recovery of 25% of control twitch tension (DUR25%$_{maint}$); time from end of injection of the maintenance doses to maximal twitch suppression (time of onset); and time from 25% to 75% twitch recovery (recovery index) after injection of the last maintenance dose. The results were calculated as mean ± SD and range. Intragroup comparison was performed by paired Student's *t*-test. Both the DUR25%$_{maint}$ values and the corresponding times of onset were related to particular events of CPB and to nasopharyngeal temperature. In those patients where more than one maintenance dose of atracurium had to be injected before or after CPB or during hypothermia, only the time of onset and the DUR25%$_{maint}$ of the last maintenance dose before the new event were used for statistical evaluation.

Results

Patient characteristics as to age, body weight, and height were 63 ± 6 yr (range 54–71), 72 ± 12 kg (range 55–86), and 168 ± 8 cm (range 152–177), respectively (10 men, 5 women). Surgical procedures were coronary artery bypass grafting ($n = 11$), aortic valve replacement ($n = 3$), and mitral valve replacement ($n = 1$). The CPB data are listed in Table 1. The intravenous injection of both the initial bolus dose and the maintenance doses of atracurium resulted in complete suppression of the twitch response in all patients. The number of maintenance doses administered before the institution of CPB was 2.5 ± 1 (1–4). The changes in time of onset of the atracurium injections and in their DUR25%$_{maint}$ in relation to specific events of CPB are shown in Table 2. The time of onset of the maintenance doses averaged 57% longer during hypothermia (<32°C) than before the institution of CPB ($P < 0.05$). Correspondingly, hypothermia almost doubled the DUR25%$_{maint}$ ($P < 0.05$). The delayed onset of the maintenance doses persisted during normothermic perfusion when the DUR25%$_{maint}$ had already returned to normal. No further change in DUR25%$_{maint}$ occurred after cessation of CPB, when the time of onset of the maintenance doses was no longer significantly different from its prebypass values. At the end of surgery, neuromuscular transmission had attained 75% of control twitch tension in all patients.

Table 1. Cardiopulmonary Bypass Data

Injection of initial dose of atracurium to start CPB (min)	92 ± 29 (50–130)
Time of start of CPB to lowest temperature (min)	19 ± 5 (15–30)
Lowest temperature (°C)	27.9 ± 2.1 (22.0–30.0)
Duration of hypothermic CPB <32°C (min)	64 ± 17 (40–95)
Start rewarming to 34°C (min)	15 ± 7 (10–22)
Duration of normothermic CPB >34°C (min)	28 ± 7 (20–45)
End of CPB to end of surgery (min)	58 ± 13 (40–80)
Total duration of CPB (min)	122 ± 30 (90–200)

CPB, cardiopulmonary bypass.
Values are mean ± SD (range); $n = 15$.

Discussion

In an attempt to quantitate the impact of hypothermic CPB on the intensity or duration of nondepolarizing neuromuscular blockade, previous workers basically resorted to one of the following three variables: (a) rate of infusion of a muscle relaxant required to maintain a predetermined constant intensity of neuromuscular blockade (1,2); (b) intensity of neuromuscular blockade in response to a preset constant rate of muscle relaxant infusion (5); and (c) intervals between repeated injection of a predetermined constant dose of a muscle relaxant administered whenever the evoked twitch tension returns to 25% of its control value (6). We adhered to the repeat injection technique to obtain data comparable to those of both a concomitantly conducted study on atracurium in noncardiac surgery patients (7) and previous communications on vecuronium in patients with CPB (6) or with neuromuscular disease (5,8).

Possible mechanisms by which hypothermic CPB interferes with nondepolarizing neuromuscular blockade include increased volume of distribution, reduced muscle perfusion, reduced biodegradation of the muscle relaxant, and functional alterations of the neuromuscular junction. The relative significance of each of these factors has been extensively discussed (5,6,9). It was concluded that the modifications of neuromuscular blockade by hypothermic CPB may be attributed to low body temperature rather than to other factors of the bypass (6) and that hypothermia may act at the level of the neuromuscular junction and the contractile apparatus of the muscle cells

Table 2. Time of Onset and Duration of Action of Maintenance Doses of Atracurium (0.6 × ED_{95} = 138 μg/kg) Injected Intravenously on 25% Recovery of the Evoked Twitch Tension After an Initial Dose of 2 × ED_{95} (460 μg/kg) During Cardiopulmonary Bypass With Hypothermia

	Time of onset (min)	$DUR25\%_{maint}$ (min)	No. of patients
Before CPB	2.1 ± 0.6 (1.0–3.5)	24 ± 4 (17–30)	15
Start of CPB to lowest temperature	2.7 ± 0.9 (2.0–4.0)	—[a]	10[b]
During hypothermic CPB (<32°C)	2.9 ± 0.9[c] (2.0–5.0)	45 ± 8[c] (35–60)	15
During rewarming	3.3 ± 0.9[c] (2.0–4.8)	—[a]	13[b]
During normothermic CPB (>34°C)	2.8 ± 1.1[c] (2.0–5.0)	22 ± 3[d] (15–26)	15
After CPB	2.3 ± 0.4[d] (1.8–3.0)	23 ± 3[d] (19–34)	15
Recovery index		17 ± 7 (8–27)	15

CPB, cardiopulmonary bypass; $DUR25\%_{maint}$, time from end of injection of the maintenance doses to recovery of 25% of control twitch tension; ED_{95}, effective dose for 95% depression of twitch tension.

[a] Not applicable, because times of cooling and rewarming are shorter than $DUR25\%_{maint}$.

[b] Injection of a maintenance dose during the process of cooling or rewarming was not required in all patients.

[c] $P < 0.05$ versus corresponding value before CPB.

[d] NS versus corresponding value before CPB.

rather than at the level of drug metabolism (9). Yet, owing to the lack of information on both pharmacokinetic and possible ultrastructural effects of hypothermic CPB, these views remain to be proved. Although our method was confined to twitch recording, the discrimination between distinct periods of the CPB may contribute to a better understanding of its effects on neuromuscular blockade.

The prolongation of the time of onset of the maintenance doses observed promptly on the institution of CPB suggests an increased volume of distribution as its causative factor. However, the onset of the maintenance doses was further retarded by cooling but was accelerated again during subsequent normothermic perfusion (>34°C). Thus, besides an increased volume of distribution, low body temperature appears to be an additional factor affecting neuromuscular blockade. Reduced temperature may interfere with neuromuscular transmission by reduced muscle perfusion or by functional impairment of the neuromuscular junction. Our present knowledge does not allow a precise understanding of the role of each of these factors. Yet, the delayed onset of action of the maintenance doses at low body temperature is not compatible with an increased bioavailability of atracurium, which previous reports (1,2) proposed to account for the increased neuromuscular blocking potency of atracurium during hypothermic CPB. The alleged significance of reduced biodegradation of atracurium was also doubted when a hypothermia-related prolongation of the $DUR25\%_{maint}$ was recorded with both pancuronium and vecuronium (6), which are known not to undergo significant biodegradation (10).

Like all previous studies on muscle relaxants and CPB, our study does not confer a reference value for the recovery index, nor can a true control group of hypothermic patients without CPB be studied in cardiac surgery. The recovery index may therefore be compared with corresponding data of a concomitantly conducted study on repeated atracurium injection in 10 noncardiac surgery patients (7). Relative to this reference value of 12 ± 5 min, the recovery index after hypothermic CPB was 42% longer, indicating some impairment of neuromuscular transmission extending beyond the duration of the bypass. In contrast to atracurium, the prolongation of the $DUR25\%_{maint}$ of pancuronium was reported to be only poorly attenuated by rewarming, with only 2 of 10 patients having attained 75% of the control electromyogram amplitudes (6). With vecuronium, the prolongation of the $DUR25\%_{maint}$ was found to be more efficiently attenuated by rewarming than with pancuronium, and at the end of surgery, only 5 of 10 patients had failed to attain 75% of control neuromuscular transmission (6). Thus, when comparing our results with previous findings (6), the impact of hypothermic CPB on neuromuscular blockade appears to be reversible in the following order: atracurium, vecuronium, pancuronium. As in neuromuscular disease (8,11), the recovery index would then be a more sensitive indicator of impaired neuromuscular transmission than $DUR25\%_{maint}$.

In conclusion, when atracurium was administered by repeated injection before, during, and after CPB, both the time of onset and the DUR25% of the maintenance doses were significantly longer during hypothermic than normothermic CPB. The $DUR25\%_{maint}$ and the time of onset of the maintenance doses returned to normal during normothermic perfusion and after cessation of CPB, respectively, whereas the recovery index remained significantly longer after CPB than reported in noncardiac surgery patients. The joint effects of an increased volume of distribution, reduced muscle perfusion, and functional impairment of the neuromuscular junction secondary to hypothermia most likely explain our results.

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Effects of Surgical Stress and Volatile Anesthetics on Left Ventricular Global and Regional Function in Patients With Coronary Artery Disease

Evaluation by Computer-Assisted Two-Dimensional Quantitative Transesophageal Echocardiography

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We investigated the effects of halothane, enflurane, and isoflurane on central hemodynamics and left ventricular global and regional function when used to control intraoperative hypertension in 39 patients with coronary artery disease. Left ventricular short-axis, midpapillary images were obtained by transesophageal echocardiography. Using a centerline algorithm, we analyzed left ventricular images for global area ejection fraction (GAEF) and segmental area ejection fraction (SAEF). The SAEF/GAEF ratio was calculated for each of eight segments. Measurements were performed after induction of anesthesia but before skin incision; 1 min after sternotomy; and during administration of the inhaled anesthetic. The increase in arterial blood pressure during sternotomy was due to an increase in vascular resistance accompanied by increases in heart rate and filling pressures while GAEF decreased. No changes in the SAEF/GAEF ratio appeared during sternotomy. The inhaled anesthetics restored arterial blood pressure by a similar decrease in vascular resistance. Isoflurane caused an increase in cardiac index that was not seen with halothane or enflurane (halothane vs isoflurane, $P < 0.05$). The GAEF was decreased by halothane but unaffected by isoflurane and enflurane (halothane vs enflurane; $P < 0.05$). Isoflurane induced a decrease in the SAEF/GAEF ratios of two segments corresponding to the inferolateral wall of the left ventricle that was, in one of these segments, significantly more pronounced compared with both halothane and enflurane. Halothane or enflurane did not cause any change in regional wall motion. We conclude that isoflurane is more likely to cause regional wall motion changes than halothane or enflurane in patients with coronary artery disease.

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Patients undergoing coronary artery surgery during low- or high-dose opioid anesthesia may experience systemic vasoconstriction, tachycardia, and intraoperative hypertension in response to sternotomy that will increase myocardial oxygen demand (1–7). Surgical stress in these patients has also been shown to increase myocardial oxygen extraction, indicating that the autoregulatory myocardial blood flow response does not meet the increased metabolic demand (4–7). This unfavorable effect on the myocardial oxygen supply/demand ratio by intraoperative hypertension may induce myocardial ischemia irrespective of the opioid dose used (1,2,4,5,7,8).

One approach to control intraoperative hypertension and to decrease myocardial oxygen demand is to use inhaled anesthetics to increase the depth of anesthesia. Roizen et al. (9) found that halothane and enflurane both effectively decreased pulmonary capillary wedge pressure (PCWP) and systemic vascular resistance (SVR) when used to treat intraoperative hypertension. Hess et al. (3), however, demonstrated that halothane-induced restoration of arterial blood

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pressure during surgical stress in patients with coronary artery disease was accompanied by a further increase in PCWP and found no change in SVR, in striking contrast to isoflurane, which acted as an afterload-reducing agent. Cardiometabolic and coronary hemodynamic measurements were not performed in these two studies.

O'Young et al. (6) and Sahlman et al. (7) studied the myocardial circulatory and metabolic effects of isoflurane as an adjunct to opioid/nitrous oxide anesthesia used to treat intraoperative hypertension in patients with coronary artery disease. The former group demonstrated that isoflurane was safe and caused no electrocardiographic (ECG) signs or metabolic evidence of myocardial ischemia. Sahlman et al. (7), however, using higher concentrations of isoflurane, showed that a normalization of intraoperative hypertension with isoflurane was associated with a significant heart rate (HR) increase and lactate production in some patients. Halothane has also been studied in this situation and was found to induce myocardial ischemia in some patients but to improve regional myocardial lactate metabolism in others (10). To our knowledge, there is no study on the cardiometabolic and coronary hemodynamic effects of enflurane when used to treat intraoperative hypertension in patients with coronary artery disease.

Thus, data are lacking, and there is also some controversy concerning the effects of the different volatile anesthetics on central hemodynamics, myocardial oxygenation, and the development of myocardial ischemia when these anesthetics are used to decrease myocardial oxygen demand during surgical stress in patients with coronary artery disease. This is probably due to the fact that these anesthetics have not been compared in one randomized study. We have therefore conducted a prospective, randomized study on the effects of halothane, enflurane, and isoflurane on central hemodynamics and global and regional left ventricular function using two-dimensional transesophageal echocardiography. The three different volatile anesthetics were used to normalize intraoperative high blood pressure caused by sternotomy in patients undergoing coronary artery bypass grafting, and our aim was to evaluate whether any of the anesthetics was preferable to the others with respect to regional left ventricular wall motion.

Methods

The study was approved by the Human Ethics Committee of the University of Gothenburg. After informed consent was obtained, 39 patients scheduled to undergo elective coronary artery bypass grafting were included in the study. All patients had two- or three-vessel coronary artery disease and an ejection fraction >0.5, determined on preoperative cardioangiography. Patients with known mitral or aortic valve insufficiency were excluded from the study. All patients were being treated with β-adrenergic receptor blockers. The patient's cardiac medication, including β-blockers, was continued up to the morning of surgery.

The patients were randomly assigned to one of three groups to receive halothane ($n = 13$), enflurane ($n = 13$), or isoflurane ($n = 13$) to control intraoperative hypertension during sternotomy. The mean age in the halothane, enflurane, and isoflurane groups was 63.1 yr (range 41–76), 58.5 yr (range 36–70), and 63.1 yr (range 44–84), respectively.

The patients were premedicated with flunitrazepam (1 mg), morphine (10 mg), and scopolamine (0.4 mg). Anesthesia was induced with thiopental (4 mg/kg), followed by fentanyl. Pancuronium (0.1 mg/kg) was used as muscle relaxant. Fentanyl was administered in incremental doses during induction of anesthesia and after intubation (i.e., before the first hemodynamic measurement, up to a total amount of 15 μg/kg). Thereafter, no central nervous system depressant was administered. The patients were ventilated with 60% nitrous oxide in oxygen during the course of the study. Ventilation was controlled with $P_{CO_2} = 4.5–5.0$ kPa and $P_{O_2} > 12$ kPa.

Central Hemodynamic Measurements

An arterial cannula was placed in the left radial artery and a central venous catheter in the left subclavian vein. A Swan-Ganz thermodilution catheter (USCI, C. R. Bard Inc., Billerica, Mass.) was inserted through the right internal jugular vein and, under fluoroscopy, guided into the pulmonary artery. Continuous recordings of systolic, diastolic, and mean arterial pressure, together with systolic, diastolic, and mean pulmonary artery pressure, central venous pressure, PCWP, and ECG leads II and V_5 were obtained with a Siemens Sirecust monitoring system (Siemens AG, Erlangen, Germany) and saved on a paper strip. Thermodilution cardiac output (L/min) measurements were performed in triplicate at each measuring point. Cardiac index ($L \cdot min^{-1} \cdot m^{-2}$), stroke volume (mL), stroke volume index (mL/m^2), SVR ($mm\ Hg \cdot min \cdot L^{-1}$), and systemic vascular resistance index (SVRI) ($mm\ Hg \cdot min \cdot m^{-2} \cdot L^{-1}$) were also calculated.

Measurements of Global and Regional Left Ventricular Function by Transesophageal Echocardiography

A single-plane transesophageal echocardiographic transducer (ALOKA, 5 MHz, phased array; ALOKA

Co., Tokyo, Japan) was positioned approximately 40 cm into the esophagus and adjusted until good short-axis images of the left ventricle at the midpapillary level were obtained with an ALOKA SSD 870 echocardiography system. Images were stored on VHS videotape and later transferred to a computer system by means of a video digitizer (11) at a rate of 25 images/s. Three cardiac cycles were selected for each measurement and saved on a floppy disk. Using a digitizing tablet, the endocardial border was outlined in systole and diastole, starting at the anterior papillary muscle. Papillary muscles were not included in the outline. Systole was defined as the smallest area during the cardiac cycle and diastole as the area at the R wave on ECG. The image sequence was displayed in real time and in slow motion, with the endocardial outline superimposed on the image to certify that the endocardial border was correctly outlined. The systolic and diastolic outlines were then projected over each other and corrected for rotational movement of the heart. No correction for translational movement was made (12). Mean values of the three cardiac cycles were used for calculations. The fractional area change between diastolic and systolic areas was calculated and was called the global area ejection fraction (GAEF). Ninety-six radii were constructed using the centerline method (13), and the areas of the 96 "slices" between the systolic and diastolic contours were calculated. These slice areas were then added together to obtain eight segments representing, approximately, anterior wall (segments 1 and 2), septal wall (segments 3 and 4), inferior wall (segments 5 and 6), and lateral wall (segments 7 and 8). The area change of each segment was divided by the corresponding diastolic area to obtain an area ejection fraction for the segment, called segmental area ejection fraction (SAEF). The SAEF/GAEF ratio was then calculated for each segment.

Each digitized and stored beat was analyzed on two different occasions by the same observer who at the second attempt was unaware of the result of his previous analysis. A correlation analysis was performed on the values of GAEFs obtained on the two occasions ($r = 0.86$).

Experimental Protocol

Hemodynamic measurements, echocardiographic images, and ECG recordings were obtained at three occasions: (a) after induction of anesthesia and tracheal intubation but before skin incision (preincision); (b) 1 min after sternotomy; and (c) during addition of a volatile anesthetic in concentrations adequate to decrease mean arterial pressure to preincision levels. High inspiratory concentrations of the volatile anesthetics were used initially to induce a rapid decrease of arterial blood pressure to presternotomy levels. The inspiratory concentrations of the different anesthetics were then gradually reduced as arterial blood pressure approached and finally stabilized around the presternotomy level. Inspiratory and end-tidal concentrations of halothane, enflurane, or isoflurane were monitored using a Siemens-Elema Servo Gas Analyzer (Siemens AG). The ECG signs of myocardial ischemia were defined as ST-segment elevation >0.2 mV or ST-segment depression >0.1 mV, 80 ms beyond the J point. Mean rectal body temperature at the start of the experimental procedure was 35.8° ± 0.1°C (mean ± SEM).

Coronary Anatomy

Without knowledge of administered anesthetic, occurrence of ischemia, or intraoperative course, one of the investigators reviewed the coronary angiogram of each patient for the characteristics of steal-prone coronary anatomy: total occlusion of at least one major epicardial artery (right or left anterior descending or proximal circumflex coronary artery), collateral flow into the bed distal to the occluded artery, and a proximal stenosis (>50% diameter reduction) of the artery supplying the collateral vessels (14). The incidence of steal-prone coronary anatomy for each of the three groups was calculated.

Statistical Analysis

Values of the various hemodynamic and echocardiographic variables were subjected to a repeated-measures two-way analysis of variance (SuperAnova, Abacus Concepts Inc., Berkeley, Calif.). A means comparison contrast analysis was performed to test the interaction between experimental stage and experimental group. To evaluate the influence of the coronary artery anatomy on the results, a repeated-measures three-way analysis of variance was performed, and interactions between data were tested by a means comparison contrast analysis. Values are presented as mean ± SEM.

Results

The incidence of steal-prone coronary artery anatomy was 46% in the halothane group, 46% in the enflurane group, and 61% in the isoflurane group (differences not significant).

Effects of Surgical Stress on Central Hemodynamics, GAEF, SAEF, and the SAEF/GAEF Ratio

During sternotomy, arterial and pulmonary pressures, as well as HR, SVRI, central venous pressure,

Table 1. Effects of Inhaled Anesthetics on Central Hemodynamics

Variable	Preincision	Sternotomy	Inhaled anesthetic	*P* value		
				Hal-Enf	Enf-Iso	Iso-Hal
MAP (mm Hg)						
Iso	81.2 ± 3.8	111.9 ± 4.3	82.6 ± 2.9			
Enf	79.5 ± 4.7	120.9 ± 3.7	82.5 ± 2.6	NS	NS	NS
Hal	83.8 ± 5.4	117.9 ± 4.6	83.8 ± 5.0			
MPAP (mm Hg)						
Iso	18.5 ± 1.7	21.5 ± 1.7	22.5 ± 2.0			
Enf	16.5 ± 1.3	21.7 ± 1.7	21.3 ± 2.2	NS	NS	NS
Hal	16.6 ± 1.4	19.7 ± 1.8	20.6 ± 1.5			
PCWP (mm Hg)						
Iso	11.0 ± 1.6	16.0 ± 1.9	15.0 ± 1.5			
Enf	9.6 ± 0.7	15.9 ± 1.5	14.0 ± 2.2	NS	NS	NS
Hal	11.7 ± 1.4	16.2 ± 1.7	17.3 ± 2.0			
CVP (mm Hg)						
Iso	8.3 ± 1.1	9.5 ± 1.1	9.8 ± 1.3			
Enf	8.1 ± 0.8	11.0 ± 0.9	10.1 ± 0.9	<0.05	NS	NS
Hal	7.9 ± 1.3	8.9 ± 1.4	9.3 ± 1.3			
CI (L/min)						
Iso	1.49 ± 0.13	1.51 ± 0.14	1.76 ± 0.15			
Enf	1.32 ± 0.07	1.37 ± 0.08	1.40 ± 0.12	NS	NS	<0.05
Hal	1.34 ± 0.04	1.48 ± 0.09	1.37 ± 0.06			
HR (beats/min)						
Iso	53.1 ± 2.3	56.5 ± 2.7	60.5 ± 3.4			
Enf	51.7 ± 1.8	58.7 ± 2.7	60.7 ± 2.7	<0.05	NS	<0.05
Hal	51.4 ± 2.8	54.5 ± 2.9	51.1 ± 4.0			
SVI (mL/m^2)						
Iso	27.6 ± 2.0	26.2 ± 1.9	28.5 ± 1.7			
Enf	25.6 ± 1.5	23.7 ± 1.6	23.7 ± 2.6	NS	NS	NS
Hal	27.0 ± 1.7	27.4 ± 1.6	28.0 ± 1.6			
SVRI (mm Hg·min·L^{-1}·m^{-2})						
Iso	1140 ± 104	1614 ± 169	986 ± 106			
Enf	1252 ± 91	1869 ± 104	1241 ± 94	NS	NS	NS
Hal	1234 ± 83	1640 ± 101	1175 ± 77			

MAP, mean arterial pressure; MPAP, mean pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; CVP, central venous pressure; CI, cardiac index; HR, heart rate; SVI, stroke volume index; SVRI, systemic vascular resistance index; Hal, halothane; Enf, enflurane; Iso, isoflurane; NS, not significant.

and PCWP increased significantly, whereas no significant changes were found in cardiac index or stroke volume index (Table 1).

Sternotomy induced a decrease in the GAEF from 0.45 ± 0.02 to 0.39 ± 0.02 ($P < 0.01$); SAEF decreased significantly in five of the eight segments during sternotomy (Figure 1). The SAEF/GAEF ratio was not significantly affected by sternotomy (Figure 2).

Effects of Inhaled Anesthetics on Central Hemodynamics

When arterial blood pressure was restored to presternotomy levels, percent end-expiratory concentrations of halothane, enflurane, and isoflurane were 0.61% ± 0.14%, 0.86% ± 0.14%, and 1.03% ± 0.10% after 4.4 ± 0.48, 5.0 ± 0.87, and 4.1 ± 0.56 min, respectively. The three anesthetics reduced arterial

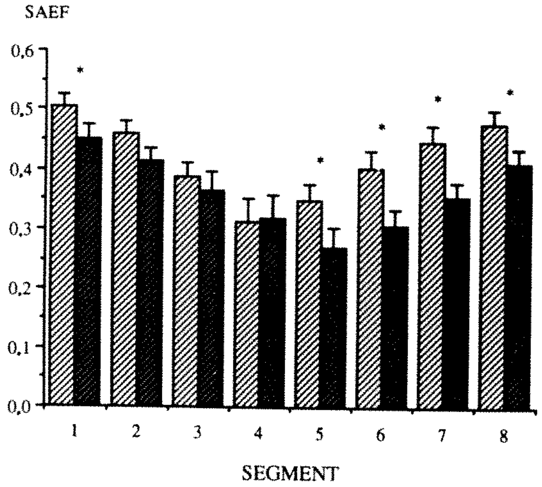

Figure 1. Effects of sternotomy on left ventricular regional wall motion. SAEF, segmental area ejection fraction. *Significant difference between preincision (▨) and sternotomy (■) ($P < 0.05$).

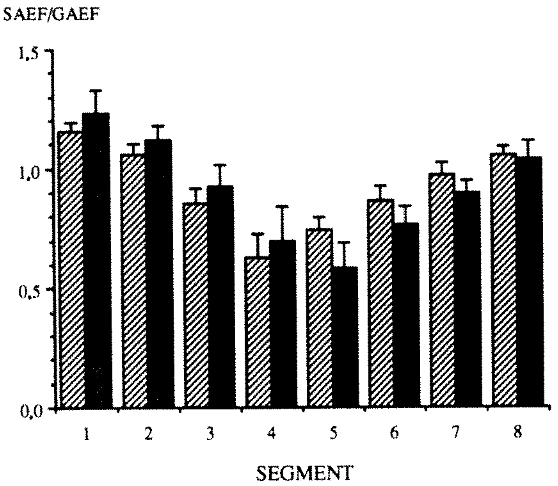

Figure 2. Effects of sternotomy on left ventricular regional wall motion. Values corrected for changes in global area ejection fraction (GAEF). SAEF, segmental area ejection fraction. Preincision (▨); sternotomy (■).

blood pressure to approximately the same extent. The restoration of arterial blood pressure to preincision levels was accompanied by a similar decrease in SVRI in the three groups. The cardiac index increased with isoflurane but did not change with halothane or enflurane (halothane vs isoflurane; $P < 0.05$). The stroke volume index was unaffected by the anesthetics. Both isoflurane and enflurane induced a small increase in HR that was significantly different from the likewise small decrease in HR caused by halothane. There were no significant differences among the groups with respect to changes in mean pulmonary artery pressure and PCWP. Changes in central venous pressure were significantly different when halothane and enflurane were compared.

Effects of Inhaled Anesthetics on GAEF and the SAEF/GAEF Ratio

Halothane caused a significant decrease in GAEF, from 0.46 ± 0.03 to 0.41 ± 0.02 ($P < 0.05$), which was not seen with isoflurane or enflurane (halothane vs enflurane; $P < 0.05$). Isoflurane induced a significant decrease in the SAEF/GAEF ratio of segments 6 and 7 ($P < 0.01$) that was significantly different when compared with halothane and enflurane ($P < 0.05$; segment 6) (Table 2, Figure 3). Halothane and enflurane did not cause any changes in the SAEF/GAEF ratio in any of the segments. There was no statistically significant interaction among type of volatile anesthetic and coronary anatomy in the halothane or enflurane groups. In the isoflurane group, however, the SAEF/GAEF ratio differed significantly between patients with steal-prone coronary anatomy ($n = 8$) and patients with other varieties of coronary anatomy ($n = 5$). Among the patients with no evidence of steal-prone coronary anatomy, isoflurane decreased regional wall motion in several segments, whereas among the patients with steal-prone coronary anatomy, regional wall motion, if anything, improved in some segments.

One patient had ECG signs of myocardial ischemia before sternotomy. In this patient, neither sternotomy nor the addition of the volatile anesthetic affected the ST segment. None of the other patients had ECG signs of ischemia during the experimental procedure.

Discussion

The baseline anesthetic in the present study was fentanyl (15 μg/kg), with the addition of nitrous oxide. A substantial hypertensive response was therefore expected, because it is known that even doses of 50–100 μg/kg are insufficient in preventing a pronounced stress-induced activation of the sympathetic nervous system and myocardial ischemia during sternotomy (2,4,5,8). In clinical practice, inhaled anesthetics are therefore used in many institutions as adjuvants to fentanyl/nitrous oxide anesthesia whenever a surgical stress response is encountered in patients with coronary artery disease. The aim of the anesthesiologist is of course to prevent or minimize the hypertensive stress response by the aid of volatile anesthetics. However, to understand the actions of these anesthetics on the cardiovascular system in this situation it is important to delineate the myocardial and circulatory effects of the inhaled anesthetics and to separate them from the effects of the surgical stress itself.

An increase in the afterload of the left ventricle during surgical stress will decrease GAEF (15). Furthermore, a general depression of myocardial contractility by (e.g., volatile anesthetics) also decreases global left ventricular function (16). Changes in SAEF during sternotomy and after the addition of volatile anesthetics could therefore to some extent be explained by changes in afterload conditions or in the contractile state of the myocardium. We have therefore used the SAEF/GAEF ratio for quantitative evaluation of regional wall motion in the present study. A decrease in this ratio during sternotomy or during the addition of volatile anesthetics would indicate a newly developed regional wall motion abnormality not necessarily caused by changes in afterload or inotropism per se. This is demonstrated in Figures 1 and 2. Sternotomy induced a significant decrease in SAEF in five of the eight segments that most likely was caused by an increase in afterload, not by re-

Table 2. Effects of Inhaled Anesthetics on the SAEF/GAEF Ratio

	Preincision	Sternotomy	Inhaled anesthetic	*P* value		
				Hal-Enf	Enf-Iso	Iso-Hal
Segment 1						
Iso	1.25 ± 0.08	1.35 ± 0.20	1.28 ± 0.14			
Enf	1.14 ± 0.06	1.13 ± 0.16	1.17 ± 0.10	NS	NS	NS
Hal	1.05 ± 0.07	1.11 ± 0.08	1.15 ± 0.04			
Segment 2						
Iso	1.12 ± 0.12	1.17 ± 0.15	1.36 ± 0.09			
Enf	1.07 ± 0.06	1.09 ± 0.05	1.21 ± 0.09	NS	NS	NS
Hal	0.98 ± 0.06	1.02 ± 0.08	1.07 ± 0.07			
Segment 3						
Iso	0.86 ± 0.07	0.82 ± 0.15	0.94 ± 0.22			
Enf	0.93 ± 0.06	0.98 ± 0.17	0.95 ± 0.15	NS	NS	NS
Hal	0.76 ± 0.15	0.97 ± 0.09	0.98 ± 0.08			
Segment 4						
Iso	0.52 ± 0.24	0.36 ± 0.36	0.72 ± 0.23			
Enf	0.73 ± 0.12	0.96 ± 0.18	0.81 ± 0.13	NS	NS	NS
Hal	0.66 ± 0.22	0.79 ± 0.11	0.91 ± 0.10			
Segment 5						
Iso	0.76 ± 0.10	0.35 ± 0.13	0.59 ± 0.11			
Enf	0.70 ± 0.10	0.75 ± 0.12	0.76 ± 0.13	NS	NS	NS
Hal	0.77 ± 0.08	0.67 ± 0.11	0.78 ± 0.07			
Segment 6						
Iso	0.91 ± 0.09	0.77 ± 0.13	0.33 ± 0.18			
Enf	0.79 ± 0.14	0.64 ± 0.15	0.74 ± 0.10	NS	<0.05	<0.05
Hal	0.89 ± 0.09	0.91 ± 0.07	0.87 ± 0.07			
Segment 7						
Iso	0.90 ± 0.09	0.96 ± 0.10	0.44 ± 0.26			
Enf	0.98 ± 0.09	0.81 ± 0.13	0.68 ± 0.22	NS	NS	NS
Hal	1.05 ± 0.08	0.91 ± 0.03	0.84 ± 0.09			
Segment 8						
Iso	0.99 ± 0.10	1.04 ± 0.10	0.89 ± 0.15			
Enf	1.07 ± 0.06	1.01 ± 0.17	0.88 ± 0.21	NS	NS	NS
Hal	1.09 ± 0.06	1.08 ± 0.10	1.03 ± 0.04			

SAEF, segmental area ejection fraction; GAEF, global area ejection fraction; Hal, halothane; Enf, enflurane; Iso, isoflurane; Segment 1–2, approximate anterior wall; Segment 3–4, approximate septal wall; Segment 5–6, approximate inferior wall; Segment 7–8, approximate lateral wall.

gional ischemia in any of the segments, because the SAEF/GAEF ratios did not change during sternotomy.

Surgical Stress, Hemodynamics, and Myocardial Function

Sternotomy caused a pronounced increase in arterial blood pressure (46%), SVR (43%), and PCWP (52%), these data confirming previous findings using an identical protocol (7,10). This was associated with a small (13%) but significant decrease in GAEF, most likely caused by an increase in the left ventricular outflow impedance. Roizen et al. (15) studied patients of advanced age and with severe signs of left ventricular dysfunction undergoing abdominal aortic aneurysm repair. Aortic cross-clamping at the supraceliac level caused an increase in aortic pressure (54%) and PCWP (38%), whereas area ejection fraction decreased by 38%. This was accompanied by frequent wall motion abnormalities not detected by conventional monitoring devices. Although the increase in loading conditions during sternotomy in the present study were comparable to that in the study by Roizen et al. (15), the decrease in GAEF was less pronounced, probably due to the fact that the preoperative left ventricular function of our patients was good. None of the patients developed ECG signs of myocardial ischemia during sternotomy, and there was no change in the SAEF/GAEF ratio, possibly due to the protective effect of the β-blockade that prevented large increases in HR and contractility.

Inhaled Anesthetics and Central Hemodynamics

The blood pressure-reducing effect of the three anesthetics was caused by comparable decreases in SVR. Hess et al. (3) could not demonstrate a halothane-

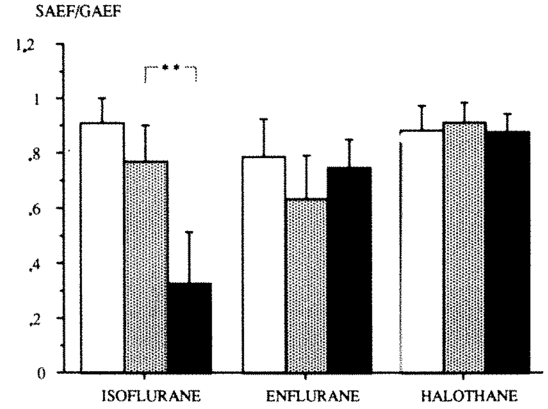

Figure 3. Regional wall motion in segment 6 (approximately inferolateral wall of the left ventricle) for the three inhaled anesthetics at the three experimental stages: preincision (□); sternotomy (▨); inhaled anesthetic (■). **Significant difference between sternotomy and inhaled anesthetic ($P < 0.01$). Halothane versus enflurane, no significant interaction between anesthetic and experimental stage. Isoflurane versus enflurane and isoflurane versus halothane, significant interaction ($P < 0.05$) between anesthetic and experimental stage. SAEF/GAEF, segmental area ejection fraction/global area ejection fraction.

induced decrease in SVR in this situation, which, however, was described by Roizen et al. (9) for both halothane and enflurane and recently by Sahlman et al. (10) for halothane. The restoration of arterial blood pressure by the inhaled anesthetics was accompanied by a significant increase in cardiac output with isoflurane, whereas no changes were seen with halothane or enflurane. These findings are in accordance with data from O'Young et al. (6) and Sahlman et al. (7,10). To our knowledge, there is no report on the effects of enflurane on systemic hemodynamics when used to treat intraoperative hypertension in patients with coronary artery disease.

Inhaled Anesthetics and Left Ventricular Wall Motion

The GAEF was only marginally affected by the volatile anesthetics, probably due to the combination of a decrease in myocardial contractility, which would decrease GAEF, and a decrease in SVR, which would increase GAEF. In the halothane group, GAEF was slightly but significantly decreased, which could be ascribed to the more marked negative inotropic effect compared with enflurane and isoflurane (17). The effects of the volatile anesthetics on regional left ventricular function were, however, clearly different. A significant decrease in the SAEF/GAEF ratio by isoflurane was seen in segments 6 and 7 but was not seen with halothane and enflurane. This was not accompanied by an overall change in stroke volume or PCWP compared with halothane or enflurane (Table 1), because dysfunction in some myocardial segments may lead to an increase in function in other segments (18).

In previous studies on myocardial, circulatory, and metabolic effects of volatile anesthetics, net lactate production has been used as "the gold standard" for diagnosing myocardial ischemia (19). It has been shown, however, that myocardial lactate metabolism is heterogenous in patients with coronary artery disease and that a significant amount of lactate can be released by the myocardium at a time when there is a net global myocardial lactate extraction (20). Net myocardial lactate production is therefore an insensitive indicator for myocardial ischemia. This was recently demonstrated by Häggmark et al. (21) who showed that only 15% of myocardial ischemic episodes were associated with net lactate production, whereas abnormal regional wall motion and ECG abnormalities were present in 83% and 44% of ischemic episodes, respectively.

Isoflurane and Myocardial Ischemia

Induction of anesthesia with isoflurane during nonsurgical conditions alone or in combination with nitrous oxide may cause ECG or metabolic evidence (net lactate production), or both, of myocardial ischemia (22–25). This has been attributed to a redistribution of coronary blood flow, coronary steal (caused by isoflurane-induced coronary vasodilatation), or isoflurane-induced hypotension in combination with tachycardia (26–29). The prerequisites for isoflurane-induced coronary steal is a steal-prone coronary artery anatomy (14). In the present study, isoflurane-induced regional wall motion abnormalities were, if anything, less pronounced in patients with steal-prone coronary anatomy and more pronounced in patients with other varieties of coronary anatomy. Although our patient population is far too small to compare the effects of different anesthetics on left ventricular regional wall motion in patients with different forms of coronary anatomy, which was not the primary aim of the study, our data do not support the hypothesis that isoflurane-induced regional wall motion abnormalities are caused by a coronary steal mechanism. Using the same protocol as in the present study, Sahlman et al. (7) showed that treatment of intraoperative hypertension with isoflurane was not associated with myocardial redistribution of flow. Instead, isoflurane-induced lactate production was associated with a combination of decreased supply and increased demand (HR increase).

Limitations

It is widely accepted that development of perioperative regional wall motion abnormalities is a sensitive and specific indicator of myocardial ischemia (30–32). It has also been demonstrated that detection of newly developed perioperative regional wall motion abnormalities is a more sensitive method than ST-segment analysis for diagnosing myocardial ischemia (30). However, all such observed changes in regional wall motion may not be entirely due to ischemia but could be ascribed to, for example, myocardial stunning or tethering of nonischemic myocardium adjacent to ischemic or infarcted myocardium (32). These nonischemic causes of regional wall motion changes would, however, tend to be evenly distributed among the three groups. Furthermore, it is theoretically possible that the isoflurane-induced hypokinesia in some of the segments, as demonstrated in the present study, was caused not only by ischemia, but by a temporal change in the ventricular wall motion pattern such that end-systole was reached earlier in one region than in another. This would be interpreted by our method as reduced wall motion in one or more segments. It is, however, not immediately obvious why this induction of temporal motion heterogeneity should be more pronounced for isoflurane compared with halothane or enflurane. Other limitations of the present study were that the clinician was aware of the study anesthetics; that the various segments were treated as independent variables, whereas these segments are physically and functionally coupled; and finally that only a single-plane, one-position transesophageal echocardiography image was used for quantification of regional wall motion.

In summary, we have studied the effects of surgical stress (sternotomy) and the inhaled anesthetics halothane, enflurane, and isoflurane on central hemodynamics and global and regional left ventricular function in patients with coronary artery disease. The sternotomy-induced increase in left ventricular outflow impedance caused a 13% decrease in GAEF, no changes in regional wall motion, and no ECG signs of myocardial ischemia. Restoration of intraoperative hypertension by the anesthetics was caused by a decrease in SVR. Isoflurane-induced control of intraoperative hypertension was accompanied by an increase in cardiac output. Isoflurane induced a depression in regional wall motion that was not seen with halothane and enflurane. These isoflurane-induced regional wall motion changes were, if anything, more pronounced in patients with other varieties of coronary anatomy than steal-prone coronary anatomy.

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Effects of Halothane and Quinidine on Intracardiac Conduction and QTc Interval in Pentobarbital-Anesthetized Dogs

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To confirm in vitro data that halothane and quinidine depressed cardiac conduction and prolonged action potential (AP) duration, the electrocardiogram and His bundle electrogram were recorded in dogs during basal pentobarbital anesthesia, after 1% halothane or quinidine (2.38 ± 0.22 μg/mL serum concentration [mean ± SEM]), or both. Purkinje fibers from a second dog were superfused with blood from the intact (support) dog, and APs were recorded. In the intact dogs, 1% halothane caused no changes in the electrocardiogram or His bundle electrogram. Quinidine prolonged QRS duration, QT interval, and rate-corrected QT ($P < 0.05$). Ventricular conduction (HS interval) slowed, and atrial effective refractory period increased ($P < 0.05$). Quinidine combined with halothane widened QRS, QT, and rate-corrected QT, prolonged the HS interval, and increased the vulnerability of the atrioventricular node to conduction block. Three of 20 dogs developed torsades de pointes-type ventricular tachycardia during simultaneous quinidine and halothane administration. In cross-superfused Purkinje fibers, the AP duration to 50% repolarization was shortened, and conduction time was prolonged by 1% halothane (both $P < 0.05$). Quinidine decreased AP amplitude, prolonged AP duration to 90% repolarization, and slowed conduction ($P < 0.05$). Quinidine combined with halothane decreased AP amplitude, and prolonged both AP duration to 90% repolarization and conduction ($P < 0.05$). When 1% halothane and therapeutic concentrations of quinidine are administered in dogs, depressed conduction and an acquired long QT syndrome with malignant ventricular arrhythmias may develop.

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Simultaneous administration of halothane and quinidine to isolated canine Purkinje fibers prolonged action potential duration (APD) and decreased conduction velocity (1). Depressed conduction can cause heart block (2), and prolongation of APD may induce arrhythmias by producing an acquired long QT interval syndrome (3,4). To confirm earlier results and test speculation concerning QT interval prolongation (1), this investigation determined the effects of halothane and quinidine on the surface electrocardiogram (ECG) and His bundle electrogram in intact dogs. Additionally, the blood cross-superfusion technique was used to correlate ECG and His bundle electrogram changes with changes in the action potentials (APs) of Purkinje fibers obtained from a second dog (5).

Blood cross-superfusion uses blood from an anticoagulated support dog to superfuse Purkinje fibers excised from another dog. A bypass circuit from the femoral artery to femoral vein of the support dog includes the tissue bath containing the Purkinje fiber. Drugs administered to the support dog subsequently bathe the excised Purkinje fiber as blood from the support dog superfuses the Purkinje fiber. Published uses of the technique include effects of both short- and long-term administration of a variety of drugs (5–7).

Methods

The local Institutional Animal Care and Use Committee approved this study, and procedures conformed to the standards described in Guide for Care and Use of Laboratory Animals (NIH publication No. (PHS) 85-23 [Rev. 1985]).

Electrocardiogram and His Bundle Electrogram Recording

Twenty (support) dogs were anesthetized with pentobarbital (30 mg/kg IV). In each experiment, the

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trachea was intubated, and the lungs were ventilated mechanically with 100% O_2 to maintain arterial CO_2 tension between 35 and 40 mm Hg. Arterial blood gases were obtained at 30-min intervals, and bicarbonate administered as needed for metabolic acidosis. The temperature of the support dog was maintained between 37° and 37.5°C with the aid of a heating lamp and heating blankets. Femoral arterial pressure was transduced and recorded.

Fluoroscopic guidance assisted the placement of 5F bipolar pacing catheters. One catheter was passed through a femoral vein into the right atrial appendage for pacing. A second catheter was placed through a femoral artery into the noncoronary cusp of the aortic valve for recording His bundle electrograms (8). The ECG (leads 1, 2, and V_1) and His bundle electrogram were recorded during sinus rhythm and at a normalized atrially paced cycle length (CL) of 400 ms (rate 150 beats/min). His bundle electrograms were filtered at 30–500 Hz and the ECGs at 0.1–100 Hz and were recorded with a Gould eight-channel recorder (Gould, Inc., Cleveland, Ohio) at paper speeds of 100 mm/s. Variables measured from the ECG included RR and PR intervals, QRS duration, and QT interval. The QT interval was corrected (QTc) for heart rate by dividing by the square root of the RR interval (9): $QTc = QT/\sqrt{RR}$.

Standard measurements were obtained from His bundle electrograms (10). The AH interval represents conduction delay within the atrioventricular node and surrounding junctional tissues (10). The AH interval was measured from the onset of the first high-frequency component of low atrial depolarization to the onset of the first high-frequency component of the His bundle spike (10–12). The HV interval, measured from the onset of the His bundle spike to the earliest point of ventricular depolarization on the His bundle electrogram (11,12), represents conduction time from the proximal His bundle to ventricular septal tissue (10). The HS interval, the time from the onset of the His bundle deflection to the latest point of ventricular depolarization on the surface ECG, represents conduction through the His-Purkinje system, the Purkinje-myocardial junction, and then through the myocardial wall itself (12,13).

The atrial effective refractory period (AERP) was determined during atrial pacing. After an eight-beat paced train at a 400-ms CL, a single extrastimulus was introduced at coupling intervals that decreased from the basic CL by 5 ms per paced train until the extrastimulus failed to capture the atrium. The longest coupling interval that failed to capture the atrium was defined as the AERP (13). Atrioventricular Wenkebach CL, the CL at which atrioventricular nodal conduction fails as a result of rate stress, was also measured (14). A slowly accelerating ramp of atrial pacing started at the underlying sinus CL, with successively decreased CLs (increased paced rates) until atrioventricular nodal conduction failed and second-degree atrioventricular block occurred. The CL at which conduction failed defined the Wenkebach CL and was determined as the average of three measurements for each experiment. Triplicate measurements were always within 10 ms.

Blood Cross-Superfusion Studies

The Purkinje fiber donor dog ($n = 20$) was anesthetized with pentobarbital (30 mg/kg IV). The trachea was intubated, and the lungs were ventilated mechanically with room air. The heart was removed rapidly through a left thoracotomy and placed in cold, oxygenated Tyrode's solution. Free-running Purkinje fibers were excised from either ventricle and placed in a Plexiglas tissue bath with a 4-mL internal volume similar to that described by Rosen et al. (5). The surface on which the Purkinje fiber rested was slanted to prevent stagnation of blood during later cross-superfusion. Multiple perfusate inlets were present to allow continuous superfusion while minimizing turbulence that could dislodge intracellular microelectrodes.

Before starting blood cross-superfusion, a peristaltic pump provided a 25-mL/min flow of Tyrode's solution through a heat exchanger into the tissue bath. The Tyrode's solution contained 137 mM NaCl, 4.0 mM KCl, 18 mM $NaHCO_3$, 1.8 mM NaH_2PO_4, 0.5 mM $MgCl_2$, 2.7 mM $CaCl_2$, and 5.5 mM dextrose. Tyrode's solution was equilibrated with a gas mixture of 95% O_2 and 5% CO_2, heated to 37°C, and had a pH of 7.40 ± 0.05.

Fibers were stimulated from one end with a bipolar Teflon-coated silver wire electrode at a CL of 500 ms (rate 120 beats/min). A stimulator pulse duration of 1 ms and a current of twice threshold were applied. Standard microelectrode techniques were used to record intracellular APs. False tendons were impaled in their midportions with glass microelectrodes filled with 3 M KCl (resistance 10–30 MΩ) and connected through a silver/silver chloride junction to the input of a WPI KS-700 dual microprobe amplifier (World Precision Instruments, New Haven, Conn.). The first derivative of the transmembrane potential was obtained with the use of an electronic differentiator that was linear between 50 and 1000 V/s.

After obtaining a stable implement, Tyrode's solution was discontinued, and blood cross-superfusion was instituted. The remaining femoral artery and vein of the support dog were cannulated, and the support dog received heparin (300 U/kg IV), before the institution of blood cross-superfusion. Blood was pumped from the femoral artery through the heat

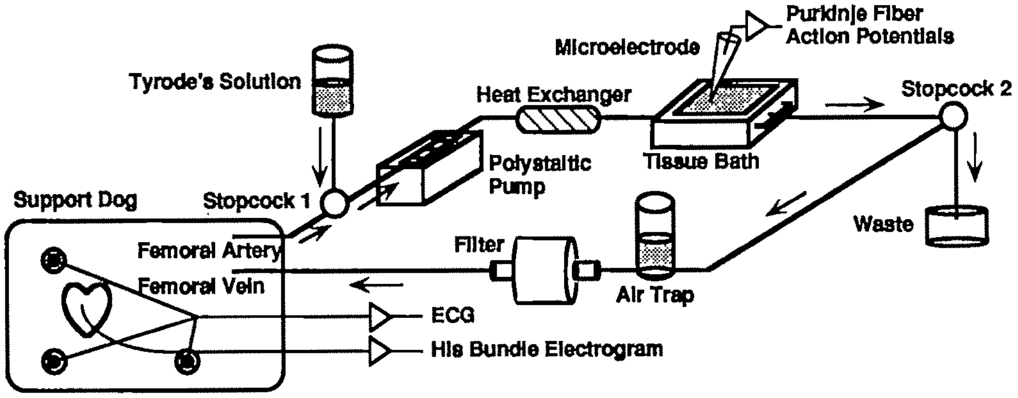

Figure 1. Diagram of blood cross-superfusion circuit. Stopcock 1 controls the selection of Tyrode's solution or femoral arterial blood from the support dog. The blood or Tyrode's solution is pumped through a heat exchanger into the tissue bath containing the excised Purkinje fiber. Stopcock 2 routes the effluent either to a discard chamber (Tyrode's solution) or through an air trap and particle filter for return to the support dog through a femoral vein cannula. The ECG and His bundle electrogram are recorded from the support dog. Action potentials are recorded from the excised Purkinje fiber in the tissue bath.

exchanger, to maintain a 37°C bath temperature, and into the bath, thus superfusing the Purkinje fiber. The effluent from the bath was collected, passed through an air trap and particle filter, and returned to the support dog. Circuit volume was 50 mL. Figure 1 shows the superfusion circuit.

Previous studies demonstrated that the change of superfusate from Tyrode's solution to blood has little effect on AP characteristics. The AP amplitude (APamp) may increase (7), as may conduction velocity (5).

The APs were photographed from an oscilloscope display, and the following measurements were performed: resting membrane potential, transmembrane potential at the onset of phase 0; APamp; APD at 50% and 90% repolarization (APD_{50} and APD_{90}, respectively); and $\dot{V}$max, maximal rate of rise of phase 0 of the AP. Conduction time (CT) was calculated as the time between the appearance of the pacer stimulus artifact and the onset of $\dot{V}$max. Data were used when a single-cell impalement was maintained for the entire experiment.

Experimental Protocol

After 1 h of stable blood cross-superfusion, control recordings of the ECG, His bundle electrogram, and AP were obtained. Halothane (1% in 100% O_2) was then administered to the support dog by inhalation. The vaporizer used was calibrated with a mass spectrogram. Through the arteriovenous bypass circuit, blood with an equivalent halothane concentration superfused the Purkinje fiber. After 1 h, measurements were repeated, and after another 1 h was allowed for halothane washout, 10 mg/kg of intravenous quinidine, followed by an infusion at 0.2 $mg \cdot kg^{-1} \cdot min^{-1}$, was administered to the support dog (15), and electrophysiologic measurements were repeated. Quinidine dosage was based on pharmacokinetic data reported by Clohisy and Gibson (15) and was intended to produce quinidine serum concentrations of 3 μg/mL. The 1% halothane was administered for 1 h while the quinidine infusion was continued and the measurements repeated. The final two data collection points, quinidine and quinidine with halothane, were alternated. Blood was withdrawn for measurement of serum quinidine (TDX Analyzer; Abbott, Inc., Irving, Tex.) and potassium (IL443 flame photometer; Instrument Laboratories, Lexington, Mass.) concentrations.

The effects of halothane and quinidine on ECG, His bundle, and Purkinje fiber data were analyzed by two-way analysis of variance for repeated measures. Significant F ratios were evaluated with Bonferroni's modification of the *t*-test (PRODAS, Conceptual Software, Houston, Tex.). A value of $P < 0.05$ was considered significant. All results are reported as mean ± SEM.

Results

Experiments involved 20 Purkinje fiber donors and 20 support dogs. Quinidine serum concentration was 2.38 ± 0.22 μg/mL; serum potassium concentration was 4.0 ± 0.3 mM. Table 1 summarizes femoral arterial pressure changes produced by halothane and quinidine administration. The combination of 1% halothane and clinically therapeutic quinidine concentrations caused significant decreases in systolic, diastolic, and mean arterial blood pressures relative to the control and 1% halothane conditions. Only the decrease in systolic pressure caused by simultaneous

Table 1. Hemodynamic Effects of Halothane and Quinidine in Dogs Anesthetized With Pentobarbital

	Control	1% Halothane	Quinidine	Quinidine + 1% halothane
Heart rate (beats/min)	122 ± 10	122 ± 5	115 ± 8	105 ± 7
Arterial blood pressure (mm Hg)				
Systolic	136 ± 8	130 ± 6	125 ± 4	100 ± 7[a]
Diastolic	100 ± 7	99 ± 5	85 ± 3	75 ± 6[b]
Mean	112 ± 7	109 ± 5	98 ± 3	84 ± 6[b]

Results presented are mean ± SEM; $n = 20$.

[a] $P < 0.05$ versus all other treatments.

[b] $P < 0.05$ versus control and 1% halothane.

Table 2. Effects of Halothane and Quinidine on the ECG and Intracardiac Electrograms During Spontaneous Sinus Rhythm in Pentobarbital-Anesthetized Dogs

Variable[a]	Control	1% Halothane	Quinidine	Quinidine + 1% halothane
RR (ms)	493 ± 41	493 ± 22	524 ± 38	569 ± 39
PR (ms)	97 ± 4	93 ± 3	101 ± 8	101 ± 4
QRS (ms)	57 ± 3	55 ± 2	66 ± 4	69 ± 5[b]
QT (ms)	243 ± 8	254 ± 9	298 ± 24	313 ± 25[c]
QTc (ms)	350 ± 11	362 ± 8	402 ± 15[c]	405 ± 9[c]
AH (ms)	69 ± 5	71 ± 2	70 ± 3	68 ± 3
HV (ms)	34 ± 2	32 ± 1	36 ± 3	35 ± 2
HS (ms)	109 ± 4	105 ± 4	118 ± 6	122 ± 5

ECG, electrocardiogram; QTc, QT interval corrected for RR (9).

Results are mean ± SEM; $n = 20$.

[a] RR and PR intervals and QRS and QT durations were measured from the surface ECG; AH, HV, and HS intervals were measured from His bundle recordings.

[b] $P < 0.05$ versus control and 1% halothane.

[c] $P < 0.05$ versus control.

Table 3. Effects of Halothane and Quinidine on the ECG and His Bundle Electrograms During Atrial Pacing in Pentobarbital-Anesthetized Dogs

Variable[a]	Control	1% Halothane	Quinidine	Quinidine + 1% halothane
PR (ms)	102 ± 6	95 ± 4	94 ± 8	103 ± 6
QRS (ms)	57 ± 2	57 ± 3	68 ± 4[b]	70 ± 5[b]
QT (ms)	250 ± 11	249 ± 8	279 ± 18	286 ± 13[b]
QTc (ms)	385 ± 17	380 ± 9	427 ± 20[b]	435 ± 16[b]
AH (ms)	79 ± 9	77 ± 5	71 ± 6	78 ± 5
HV (ms)	34 ± 1	32 ± 1	35 ± 3	35 ± 2
HS (ms)	109 ± 4	106 ± 5	124 ± 5[b]	131 ± 5[b]
AERP (ms)	155 ± 9	136 ± 15	220 ± 24[b]	203 ± 20[c]
Wenkebach CL (ms)	226 ± 10	223 ± 10	239 ± 10	263 ± 12[d]

AERP, atrial effective refractory period; CL, cycle length; ECG, electrocardiogram; QTc, QT interval corrected for RR (9); Wenkebach CL is the point of atrioventricular nodal conduction failure during rate stress.

Results are mean ± SEM; $n = 20$.

[a] PR, QRS, QT were measured from the surface ECG; AH, HV, HS intervals were measured from His bundle recordings.

[b] $P < 0.05$ versus control and 1% halothane.

[c] $P < 0.05$ versus 1% halothane.

[d] $P < 0.05$ versus all other conditions.

halothane and quinidine administration achieved significance versus the quinidine without halothane state.

Table 2 describes the effects of halothane and quinidine on the ECG and His bundle recordings during spontaneous sinus rhythm. The 1% halothane produced no significant changes in measured variables, whereas quinidine significantly prolonged only the QTc interval versus control. In contrast, the combination of quinidine and halothane prolonged QRS duration (vs control and 1% halothane administration) and QT and QTc intervals (both vs control).

Table 3 presents data at a paced CL of 400 ms. Just as during spontaneous CL, 1% halothane had no effect on the measured variables. Quinidine prolonged QRS duration and QTc and HS intervals. Additionally, quinidine increased AERP relative to the control or 1% halothane conditions. The combination of halothane and quinidine prolonged QRS duration and QT, QTc, and HS intervals versus control and 1% halothane. The AERP during halothane and quinidine only was prolonged relative to 1% halothane (203 ± 20 vs 136 ± 15 ms). Wenkebach CL increased relative to all other conditions during the simultaneous administration of halothane and quinidine, making the atrioventricular node more vulnerable to block. Changes in HS, QT, and QTc intervals and Wenkebach CL demonstrated significant interactions ($P < 0.05$) between halothane and quinidine.

Table 4 details the effects of halothane and quinidine on Purkinje fiber APs during blood cross-superfusion. Halothane 1% significantly prolonged CT, and the reduction of APD_{50} approached statistical significance ($P = 0.06$). Addition of quinidine in the absence of halothane reduced APamp and prolonged APD_{90} versus control; $\dot{V}$max decreased, although the reduction in $\dot{V}$max did not reach statistical significance; CT also increased. Combination of 1% halothane and quinidine superfusion further prolonged APD, with a significant prolongation of APD_{90} compared with control; $\dot{V}$max was further reduced, but as before, decrements were not statistically significant; CT was prolonged further during administration of halothane and quinidine ($P < 0.05$ vs control).

Figure 2 shows APs recorded from a single cell during superfusion with quinidine and halothane. Inhalation of 1% halothane shortened APD_{50} (Figure 2B) and, after superfusion with quinidine, loss of

Table 4. Effects of Halothane and Quinidine on Canine Purkinje Fibers During Blood Cross-Superfusion in Pentobarbital-Anesthetized Dogs

Variable[a]	Control	1% Halothane	Quinidine	Quinidine + 1% halothane
RMP (mV)	93.1 ± 2.3	92 ± 2.8	87.8 ± 2.7	85.8 ± 2.2
APamp (mV)	122 ± 2	121 ± 1	115 ± 2[b]	112 ± 3[b]
APD_{50} (ms)	141 ± 9	135 ± 7[c]	136 ± 8	145 ± 8
APD_{90} (ms)	213 ± 11	207 ± 8	230 ± 9[b]	246 ± 4[b]
$\dot{V}$max (V/s)	491 ± 63	482 ± 53	396 ± 44	386 ± 49
CT (ms)	3.98 ± 0.4	4.46 ± 0.39[b]	5.17 ± 0.43[b]	5.55 ± 0.45[b]

RMP, resting membrane potential; AP, action potential; APamp, AP amplitude; APD_{50}, AP duration at 50% repolarization; APD_{90}, AP duration at 90% repolarization; $\dot{V}$max, maximal rate of rise of phase 0 of the AP; CT, conduction time.

Results are mean ± SEM; $n = 20$.

[a] Paced cycle length 500 ms.

[b] $P < 0.05$ versus control.

[c] $P = 0.06$ versus control.

plateau potential, coupled with a prolongation of the terminal phase of repolarization, produced a "triangular" AP (Figure 2C). Combination of 1% halothane and quinidine (Figure 2D) further prolonged the APD and slowed conduction.

During administration of halothane and quinidine, 3 of the 20 support dogs developed torsades des pointes, and one of the three died.

Discussion

In vitro study of excised cardiac tissue to determine the electropharmacologic effects of drugs allows precise control of experimental variables such as temperature and drug concentration. However, extrapolation from such studies to the intact animal or clinical situation poses considerable problems. Blood is a heterogeneous suspension that contains epinephrine (16), thyroid hormone (17), and other electrophysiologically active components (5). Because isolated tissue is devoid of autonomic innervation, significant direct autonomic or indirect baroreceptor effects of the drugs under study may not be observed. Halothane causes significant depression of autonomic outflow at central and peripheral sites and alters baroreflex control of the cardiovascular system (18,19). Quinidine also has significant parasympathetic and α-adrenergic blocking effects (20,21). These cardiodepressant and vasodilator effects combined to produce the hypotension noted in the intact dogs in this study.

In a previous study of isolated Purkinje fibers superfused with Tyrode's solution, quinidine depressed $\dot{V}$max, prolonged APD, and depressed conduction (1). When halothane was added, resting membrane potential and APamp decreased, $\dot{V}$max decreased further, and both APD and conduction were markedly prolonged (1). Conduction block and inexcitability occurred often during the simultaneous administration of quinidine and halothane (1).

This investigation sought to confirm these observations in the more clinically relevant model of intact dogs. Inclusion of Purkinje fiber data during blood cross-superfusion allowed validation of previous work and comparison with findings in the intact animal. The objective was not reexamination of the effects of halothane/pentobarbital anesthesia on cardiac conduction. In fact, at paper speeds of 100 mm/s, the minimal expected resolution of 2.5 ms for intracardiac intervals was insufficient to differentiate the 2-ms halothane-induced increase in HV interval reported by Atlee et al. (22).

Purkinje Fiber Action Potentials

The present study estimated CT as the interval from the onset of the pacer artifact to the upstroke of the AP. This interval depends not only on conduction, but also on the excitability of the tissue depolarized by the pacing stimulus and the "liminal length" (i.e., the length of tissue that must be depolarized beyond threshold to allow propagation) (23). The effects of halothane on these properties are unknown and could complicate the interpretation of CT in the present study. Still, 1% halothane prolonged CT, consonant with previous studies (1,24,25). Both halothane-induced inhibition of the fast Na^+ channel responsible for the rapid phase 0 upstroke of the AP (24,26) and increased resistance at the gap junctions between cardiac cells may contribute (27). Depression of either $\dot{V}$max or cell-to-cell communication slows conduction in myocardium (28).

In this study, halothane shortened APD_{50} from 141 ± 9 to 135 ± 7 ms ($P = 0.06$). Previously published data concur that APD_{50} is the AP variable most affected by halothane (1,29,30). Turner et al. (31) suggested that halothane shortened the AP plateau phase by inhibition of a persistent Na^+ "window" current, although the prominent effects of halothane on slow inward Ca^{2+} current (32–34) and myocardial Ca^{2+} handling (35,36) may also contribute.

The effects of quinidine on AP variables agreed with existing data (20,37). Quinidine reduced Purkinje fiber APamp and increased CT, consistent with Na^+ channel block and shift of reactivation to more positive membrane potentials (37). The reduction in $\dot{V}$max, from 491 ± 63 to 396 ± 44 V/s (19%), did not achieve statistical significance. Prolongation of APD appears to be due to block of the delayed rectifier K^+ channel responsible for repolarization (38).

Simultaneous administration of halothane and quinidine to Purkinje fibers by blood cross-superfu-

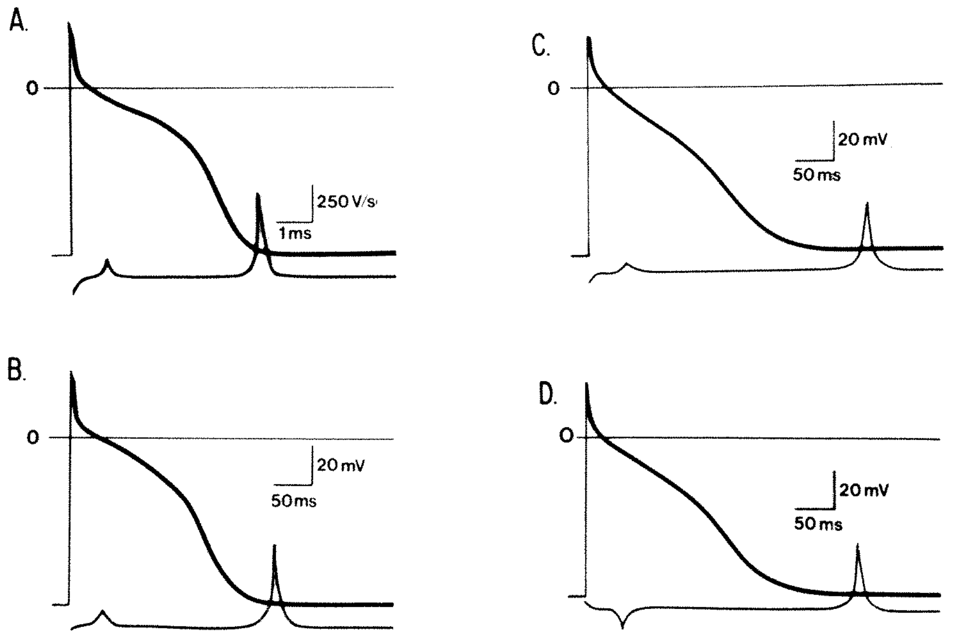

Figure 2. Effects of halothane and quinidine on canine Purkinje fiber APs during blood cross-superfusion. The *upper trace* in each panel shows a canine Purkinje fiber AP at a paced CL of 500 ms. The *lower trace* shows $\dot{V}$max for each AP at a different oscilloscope sweep speed. The amplitude of the spike is proportional to $\dot{V}$max of phase 0. The 0-mV potential line is shown in each panel. (**A**) Time and amplitude calibrations for $\dot{V}$max; (**B–D**) time and amplitude calibrations for the AP. (**A**) Normal AP during blood cross-superfusion. (**B**) 1% Halothane has been added and the plateau shortened. (**C**) Quinidine produced triangulation of the AP with prolongation of APD$_{90}$; $\dot{V}$max decreased and conduction slowed. (**D**) Effects of 1% halothane and quinidine during blood cross-superfusion; loss of APamp and further prolongation of APD$_{90}$ are evident.

sion confirmed previous observations (1). Quinidine and halothane decreased APamp, and prolonged both APD$_{90}$ and CT. However, the present data did not evince the synergistic interaction between halothane and quinidine previously reported (1).

Electrocardiogram

In the current study, halothane had no significant effect on the ECG or His bundle electrogram. Previous investigators concluded that halothane prolongs the QT interval in dogs and humans (39,40). In dogs, Riley et al. (39) found that 2% halothane prolonged the QT interval relative to the awake state. The QT interval prolongation in the presence or absence of autonomic block demonstrated a direct effect of halothane on repolarization independent of changes in autonomic tone (39).

Differences between the current study and previous investigations (39,40) may reflect the use of 1% halothane or the presence of basal barbiturate anesthesia in the current study. Thiopental prolongs the QT interval (41,42), and pentobarbital prolongs repolarization during blood cross-superfusion (5). McConachie et al. (41) demonstrated in patients that preexisting barbiturate-induced QT interval prolongation abolished the expected incremental increase in repolarization produced by enflurane or isoflurane. However, Hart et al. (43) showed that 1.13% halothane prolonged QT interval in dogs despite basal pentobarbital anesthesia.

Although quinidine significantly increased only QTc during spontaneous sinus rhythm (Table 2), during rate-normalized pacing, prolongation of QRS duration and HS interval reflected slowed conduction. Increased QT and QTc intervals demonstrated prolonged repolarization (20,37).

Intracardiac Electrogram

Elegant work by Atlee et al. (22) showed that 1.2 MAC halothane increased the AH, HV, and HS intervals compared with the awake state in chronically instrumented dogs. Abolition of AH interval prolongation by autonomic blockade demonstrated an indirect sympatholytic effect of halothane on the AV node (22). However, in an otherwise similar study, the same group reported no change in heart rate or AH interval when anesthesia was induced with halothane (14). The authors speculated that differences in intrinsic sympathetic tone, indicated by different baseline heart rates in the two studies, may have been responsible (14). In an isolated guinea pig heart preparation, Gallenberg et al. (44) demonstrated no prolongation of atrioventricular conduction time by 1% halothane.

Basal pentobarbital anesthesia in the present study contrasts with previous studies (14,22,44). Pentobarbital anesthesia increased heart rate and HV interval in chronically instrumented dogs (45). Addition of 1% halothane to basal pentobarbital anesthesia in dogs increased AH interval (61 ± 3 to 67 ± 5 ms), whereas heart rate decreased from 167 ± 7 to 147 ± 7 beats/min (46); HV interval did not change (46). After vagotomy, halothane produced no change in heart rate or AH interval (46). Morrow et al. (46) concluded that the slowed heart rate prolonged the AH interval. Ammendrup and Atlee (47) described a slowed heart rate, increased AH and HV intervals, and no change in HS interval when dogs anesthetized with pentobarbital breathed 1% halothane. However, Turner et al. (48) showed that basal pentobarbital anesthesia abolished halothane-induced depression of epicardial activation time, a variable analogous to the HV interval. Hart et al. (43) found prolonged AH intervals and slowed heart rates without changes in HV interval during inhalation of halothane by pentobarbital-anesthetized dogs. Blood pressure was maintained by phenylephrine infusion (43). Thus, prolongation of HV interval by halothane during pentobarbital anesthesia is controversial. Prolongation of AH interval occurs when heart rate slows (46) and probably represents sympatholytic effects of halothane. In the present study, heart rate and arterial pressure were unchanged after halothane administration. This indicated minimal reduction in sympathetic tone and suggested that little change in AH interval or arterial pressure could be expected.

Effects of halothane on Wenkebach CL and AERP have been reported previously. At a paced CL of 500 ms, increasing doses of halothane did not alter AERP in dogs but shortened AERP at faster paced rates (300 ms CL) (49). Atlee and Yeager (14) found no change in Wenkebach CL or AERP in autonomically intact dogs after administration of halothane and an increased Wenkebach CL after autonomic block. Gallenberg et al. (44) found no halothane-induced increase in Wenkebach CL in isolated guinea pig heart. Hart et al. (43) added further confusion by showing that Wenkebach CL decreased from 280 ± 7.6 to 241 ± 6.3 ms when halothane was inhaled by pentobarbital-anesthetized dogs. The absence of effect in the present study is not surprising.

As anticipated (20,37), quinidine significantly prolonged AERP and Wenkebach CL. Prolongation of HS interval was noted above.

Halothane and Quinidine

The combined effects of halothane and quinidine confirmed previous in vitro results (1) and demonstrated a potential for conduction abnormalities in both the atrioventricular node, indicated by the synergistically increased Wenkebach CL, and the ventricle, suggested by the synergistically increased HS interval.

The occurrence of torsades des pointes in three dogs receiving halothane and quinidine illustrated the arrhythmogenicity of prolonged repolarization (4). Prolongation of the QT interval actuates oscillatory inward currents during the protracted plateau phase of the AP (50). These result in membrane potential oscillations called early afterdepolarizations and typically produce torsades des pointes-type ventricular tachycardia (3). In addition, drug-induced slowing of conduction, as observed in this study, may produce a critical area of myocardium that acts as a substrate for reentrant ventricular tachycardia (3). Prolongation of repolarization and slowing of conduction by halothane and quinidine could exacerbate arrhythmias by either mechanism.

Published clinical reports describe life-threatening arrhythmias and death during anesthesia in patients with congenital prolongation of the QT interval (51). Riley et al. (39), on the basis of their observation of QT interval prolongation by volatile anesthetics in dogs, advised caution during the administration of volatile anesthetics to patients with QT interval prolongation. The present data suggest that patients with pharmacologically induced QT interval prolongation may also be at increased risk during anesthesia, especially if halothane is used.

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Differences in pH Management and Pulsatile/Nonpulsatile Perfusion During Cardiopulmonary Bypass Do Not Influence Renal Function

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The renal effects of pulsatile (pulse pressure 18.0 ± 1.5 mm Hg [mean ± SEM]) or nonpulsatile perfusion (mean pulse pressure 1.9 ± 0.4 mm Hg) during either α-stat (mean Pa_{CO_2} 41.2 ± 0.9 mm Hg measured at 37°C) or pH-stat (mean Pa_{CO_2} 60.6 ± 1.7 mm Hg measured at 37°C) pH management of hypothermic cardiopulmonary bypass (CPB) were studied in 100 patients undergoing elective coronary artery bypass surgery. Mean urine output, fractional excretion of sodium and potassium, and renal failure index all increased during the study period; however, there was no difference among the four different CPB management groups. Mean postoperative creatinine and blood urea nitrogen values decreased compared with preoperative values, again without differences among treatment groups. Three patients developed acute renal insufficiency; of these, two had received nonpulsatile perfusion and pH-stat management, and the other had been managed with pulsatile perfusion and pH-stat management. These three patients all had undergone prolonged CPB and required at least two vasoactive drugs and the use of an intraaortic balloon pump to be weaned from CPB. In patients with normal preoperative renal function undergoing hypothermic CPB, neither the mode of perfusion, pulsatile or nonpulsatile, nor the method of pH management, pH-stat or α-stat, influences perioperative renal function.

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Recent debate (1) concerning optimal pH management during cardiopulmonary bypass (CPB) has centered on the resulting cerebral perfusion (2) and the implications for postoperative neurologic outcome (3,4). Similar controversy with respect to the use of pulsatile or nonpulsatile perfusion has focused on the function of other organs such as the kidney. In this regard, conflicting results as to the benefit of the use of the more physiologic pulsatile perfusion were obtained in the 1970s, with both improved (5,6) and unchanged renal function being observed (7,8). Kastl-Killinger et al. (9) have renewed interest in this issue after demonstrating increased urine output (U/O) when using pulsatile perfusion in seven patients undergoing CPB for coronary artery bypass (CAB) surgery. The effect of pH management on renal function has not been investigated as extensively, although two recent studies have suggested improved renal function with α-stat, as opposed to pH-stat, pH management during nonpulsatile CPB (10,11). However, in all of these studies, the renal effects of either pulsatile or nonpulsatile perfusion, or pH-stat or α-stat pH management, were investigated independently of each other.

The purpose of this study was therefore to investigate the renal effects of pulsatile or nonpulsatile perfusion during either α-stat or pH-stat pH management in patients undergoing hypothermic CPB for CAB surgery.

Methods

The study was begun after institutional approval and written, informed consent were obtained. As part of an ongoing study evaluating neuropsychologic outcomes, patients undergoing elective CAB surgery were randomly assigned to one of four treatment groups to receive either pulsatile or nonpulsatile perfusion and either pH-stat or α-stat pH management during hypothermic CPB. This randomization was stratified according to surgeon ($n = 4$), to account for differences in technique. Patients were included in this portion of the study if they had not received a diuretic on the operative day (either preoperatively or intraoperatively) or if they had abnormal renal func-

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tion, defined as blood urea nitrogen (BUN) >10.7 (women) or >12.1 (men) mmol/L, or creatinine >124 (women) or >168 (men) μmol/L (the upper ranges of normal in our laboratory, where 1 mmol/L BUN = 2.8 mg%, and 1 μmol/L creatinine = 0.011 mg%).

Patients received an opioid or benzodiazepine, or both, as premedication. Anesthesia consisted of a high-dose opioid (fentanyl [50–100 μg/kg] or sufentanil [10–20 μg/kg]), benzodiazepine (midazolam), nondepolarizing muscle relaxant (vecuronium or pancuronium), and air/oxygen. A five-lead electrocardiogram, radial artery blood pressure, pulmonary artery blood pressure, and U/O were continuously monitored. Arterial blood gas analysis was performed using a Radiometer ABL2 analyzer. For α-stat management during CPB, arterial blood gas was measured at 37°C and CO_2 was adjusted to maintain a $Paco_2$ of 40 mm Hg. For pH-stat management, arterial blood gas was measured at 37°C and corrected to the patient's nasopharyngeal temperature using the Kelman-Newman nomogram, and exogenous CO_2 was adjusted to maintain a temperature-corrected $Paco_2$ of 40 mm Hg. Simultaneous blood and urine samples were collected intraoperatively before CPB, during hypothermic CPB, during normothermic CPB, and after discontinuation of CPB. To obtain appropriate samples, the urine was collected after emptying the existing urine from the urometer. This allowed determinations to be made of the fractional excretion (Fe) of sodium ($Fe_{Na} = U/P_{Na} \div U/P_{Cr} \times 100$) or potassium ($Fe_K = U/P_K \div U/P_{Cr} \times 100$), as well as renal failure index (RFI $= U_{Na} \div U/P_{Cr}$), where U is urine concentration, P is plasma concentration, and Cr is creatinine (12). Measurements of BUN and creatinine were also made preoperatively as well as on the first and second mornings postoperatively.

All operations were performed through a median sternotomy. Anticoagulation was produced using 300–400 U/kg of heparin before aortic cannulation. Additional heparin was added as necessary to maintain the activated clotting time >400 s. Cold crystalloid cardioplegia without mannitol was used for myocardial preservation by two of the surgeons, whereas cold blood cardioplegia without mannitol was used by the other two. A Cobe Stockert roller pump and a Bard hollow-fiber membrane oxygenator were used for CPB. The circuit was primed with 2.3 L of lactated Ringer's solution to which 100 mEq of sodium bicarbonate and 5000 U of heparin were added. Pump flows of 2.0–2.5 $L \cdot min^{-1} \cdot m^{-2}$ were used, with mean arterial pressure maintained between 50 and 80 mm Hg using isoflurane or phenylephrine as necessary. Pulsatile perfusion was produced using a Cobe Flow Controller II at a rate of 65 pulses/min, by maintaining systole approximately equal to 65% of the cycle time, adjusted as necessary to produce maximal pulse pressures (PP). The PP was measured via a radial arterial line and recorded on a Hewlett Packard Merlin monitor, which uses a five-beat averaging program. Pulsatile perfusion was limited to the period during which the aortic cross-clamp was in situ (hypothermic CPB). This was necessary because cross-clamp removal and the institution of rewarming frequently led to the resumption of cardiac ejection, which could not be effectively synchronized with the pump pulsations. After discontinuation of CPB, heparinization was reversed using protamine in a dose of 1 mg per active unit of heparin.

Demographic data were compared using one-way analysis of variance with χ^2 analysis for comparison of gender distribution. Intraoperative variables were analyzed with one-way analysis of variance, whereas measurements of renal function were analyzed using repeated measures analysis of variance with Student-Newman-Keuls post hoc testing when differences were found. A P value <0.05 was considered statistically significant.

Results

One hundred six patients undergoing elective CAB surgery were enrolled in the study. Six patients received diuretics intraoperatively and were excluded from data analysis, leaving 100 patients. Their demographic data are listed in Table 1. There were no statistically significant differences among the four groups with respect to patient age, height, weight, gender distribution, number of vessels grafted, or duration of CPB. There was also no difference in the intraoperative use of dopamine among the four groups.

The CPB values obtained during aortic cross-clamping (hypothermic CPB) are listed in Table 2. It can be seen that in the pulsatile groups, an average PP of approximately 20 mm Hg, at a rate of approximately 67 pulses/min, was achieved. This was significantly different from the nonpulsatile groups ($P < 0.001$). The pH and $Paco_2$ values are shown as measured at 37°C; those for the α-stat groups were approximately 7.42 and 37 mm Hg, respectively, and were significantly different ($P < 0.001$) from those same indices in the pH-stat groups. Four significantly different treatment groups were therefore produced.

The U/O before CPB and that during CPB for the four groups are shown in Figure 1. Although there was a statistically significant increase in U/O during CPB, there were no differences among the groups separately or when pulsatile was compared with nonpulsatile perfusion or α-stat with pH-stat management. Figures 2–4 show the fractional excretion of

Table 1. Clinical Characteristics of 100 Patients Undergoing Elective Coronary Artery Bypass Surgery

	Pulsatile perfusion		Nonpulsatile perfusion	
	α-Stat (n = 27)	pH-Stat (n = 22)	α-Stat (n = 26)	pH-Stat (n = 25)
Age (yr)	60.9 ± 1.6	61.3 ± 1.7	59.4 ± 1.3	61.1 ± 1.4
Weight (kg)	88.4 ± 2.7	82.0 ± 2.6	82.9 ± 2.4	87.6 ± 3.5
Height (cm)	170.5 ± 1.9	170.9 ± 2.1	170.6 ± 1.4	170.5 ± 2.1
Gender (M/F)	23/4	19/3	24/2	20/5
No. of grafts	2.9 ± 0.1	3.1 ± 0.2	2.8 ± 0.2	2.8 ± 0.1
CPB time (min)	91.1 ± 5.8	99.1 ± 5.5	89.8 ± 5.2	98.6 ± 6.2

CPB time, duration of cardiopulmonary bypass; M, male; F, female.
Values are mean ± SEM; no significant differences among groups.

Table 2. CPB Values During Aortic Cross-Clamping in the Four Study Groups

	Pulsatile perfusion		Nonpulsatile perfusion	
Variable	α-Stat (n = 27)	pH-Stat (n = 22)	α-Stat (n = 26)	pH-Stat (n = 25)
Time (min)	47.3 ± 3.6	52.5 ± 3.3	47.3 ± 3.3	46.9 ± 3.1
Temp (°C)	28.9 ± 0.3	28.2 ± 0.1	28.7 ± 0.2	28.7 ± 0.4
MAP (mm Hg)	68.8 ± 2.0	63.3 ± 2.5	70.4 ± 2.5	69.1 ± 2.7
PP (mm Hg)	18.6 ± 1.6^a	17.3 ± 1.4^a	2.0 ± 0.4	1.7 ± 0.3
Rate (min^{-1})	67.3 ± 1.8^a	66.8 ± 1.4^a	167.5 ± 9.6	191.7 ± 6.4
pH^b	7.43 ± 0.01	7.26 ± 0.01^a	7.42 ± 0.01	7.25 ± 0.01^a
Pa_{CO_2} (mm Hg)^b	37.0 ± 0.7	59.9 ± 1.8^a	37.1 ± 1.0	61.2 ± 1.5^a

CPB, cardiopulmonary bypass; Time, duration of cross-clamp; Temp, temperature; MAP, mean arterial pressure; PP, pulse pressure; Rate, pulse rate.
Values are mean ± SEM.
[a] $P < 0.001$.
[b] As measured at 37°C.

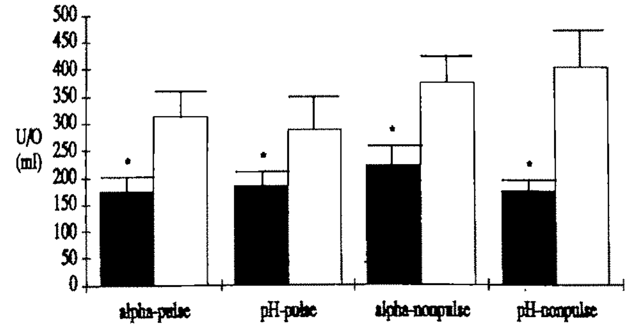

Figure 1. Urine output (U/O) before (*filled bars*) and during (*open bars*) cardiopulmonary bypass (CPB). Values are mean ± SEM. *Prebypass versus CPB; $P < 0.001$; no significant differences among groups. alpha, α-stat; pulse, pulsatile perfusion; pH, pH-stat; nonpulse, nonpulsatile perfusion.

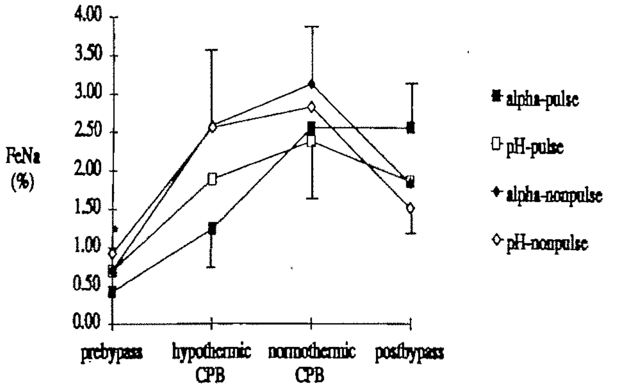

Figure 2. Fractional excretion of sodium (FeNa) at the four measurement times. Values are mean ± SEM. *Prebypass versus other times; $P < 0.001$; no significant differences among groups. Other abbreviations as in Figure 1.

sodium and potassium and the RFI as a function of time for each of the four groups. Although there was a statistically significant and progressive increase of these variables during the study period, again, there were no differences among the four groups or between the two treatment options when compared independently. Comparisons between preoperative and postoperative BUN and creatinine are shown in Figures 5 and 6. Again, there was no difference between treatments, although both variables decreased significantly in the postoperative period. There was a slight but statistically significant difference in postoperative creatinine when α-stat-group and pH-stat-group patients were compared (85 ± 20 [mean ± SEM] vs 89 ± 24 μmol/L; $P < 0.05$). Three patients developed acute renal insufficiency (ARI)

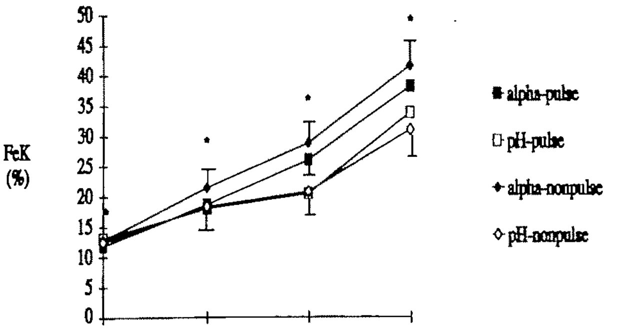

Figure 3. Fractional excretion of potassium (FeK) at the four measurement times. Values are mean ± SEM. *Each measurement versus other times; $P < 0.001$; no significant differences between groups. Other abbreviations as in Figure 1.

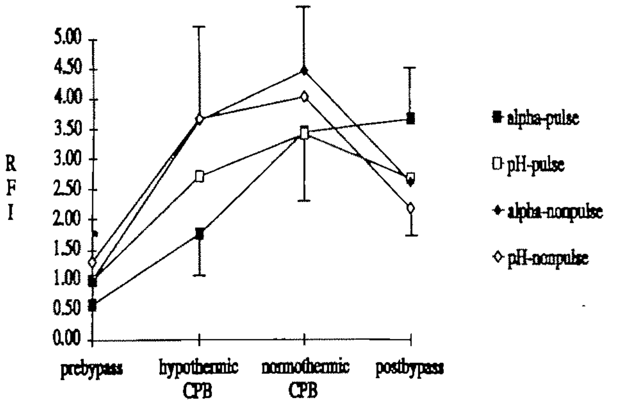

Figure 4. Renal failure index (RFI) at the four measurement times. Values are mean ± SEM. *Prebypass versus other times; $P < 0.001$; no significant differences between groups. Other abbreviations as in Figure 1.

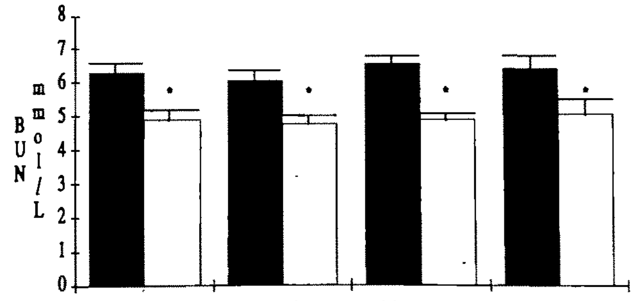

Figure 5. Preoperative (*filled bars*) and postoperative (*open bars*) blood urea nitrogen (BUN). Values are mean ± SEM. *Preoperative versus postoperative; $P < 0.001$; no significant differences between groups. Other abbreviations as in Figure 1.

within the first 48 h postoperatively, defined as BUN or creatinine outside the upper range of normal in our laboratory (see earlier text). Two of these patients underwent nonpulsatile perfusion and pH-stat management; the other underwent pulsatile perfusion and pH-stat management. By χ^2 analysis, pH-stat management was not statistically worse than α-stat management ($P = 0.06$). These three patients were older than the average, having a mean age of 65.7 ± 4.0 yr. Their mean cross-clamp times of 61.7 ± 6.5 min and total duration of CPB of 167.7 ± 11.9 min were also longer than average. These patients all required inotropic support and the use of an intraaortic balloon pump to allow weaning from CPB. Use of an intraaortic balloon pump was significant ($P < 0.001$) as a marker for developing ARI, because three of five patients in this study requiring an intraaortic balloon pump developed ARI.

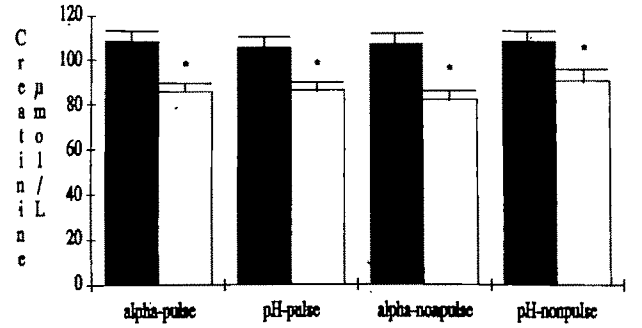

Figure 6. Preoperative (*filled bars*) and postoperative (*open bars*) creatinine. Values are mean ± SEM. *Preoperative versus postoperative; $P < 0.001$; no significant differences between groups. Other abbreviations as in Figure 1.

Discussion

The demographics of our patients are representative of those undergoing elective CAB surgery. Our incidence of ARI of 3% is also consistent with that reported by other groups (13,14). Although we were able to produce the four possible treatment options of pH management and pulsatile/nonpulsatile perfusion, we were unable to show clear superiority of one combination over the others with respect to renal function. However, it was shown that α-stat management did result in a slightly lower mean postoperative creatinine value compared with pH-stat management and that the three patients who developed ARI had all received pH-stat management, although this was not statistically significant ($P = 0.06$).

The influence of pH management, either α-stat or pH-stat, on renal function has also been examined in two previous studies. Michielon et al. (10) studied 201 patients, and although they noted increased U/O in the α-stat group, they found no differences in fractional excretion of sodium and RFI and believed that they could not claim superiority for α-stat management. The second study, by Tuppurainen et al. (11), found no difference in inulin clearance between their α-stat and pH-stat groups. Inulin clearance did, however, correlate with systemic oxygen uptake, which in turn was correlated with arterial pH. Because the higher pH during α-stat management yielded increased oxygen uptake, they therefore concluded that inulin clearance and thus renal function was better preserved with α-stat management. These subtle differences in renal function are clinically inconclusive but are similar to our findings. In contrast to these findings is an animal study in which no differences in renal blood flow, as measured using microsphere injections, were observed when α-stat and pH-stat management were compared (15).

The pulsatile/nonpulsatile debate during the 1970s ended without a clear resolution with respect to the effects on renal function, because various studies showed improvements as well as no effect (16). The recent report by Kastl-Killinger et al. (9), in which atrial natriuretic peptide levels were measured, again reported improved renal function with pulsatile perfusion. This was defined as increased atrial natriuretic peptide and U/O that resulted from a PP of 25 mm Hg. Their conclusions, however, were based on a total of only 14 patients, 7 of whom received pulsatile perfusion, and all of whom were normotensive and not receiving β-adrenergic blocker therapy. Our findings are, however, based on 100 patients, most of whom were receiving β-blockers and are therefore likely to be more representative of the current CAB surgery population.

Which, if any, of the characteristics of the pulse wave are important for end-organ perfusion is unclear. The mean PP of 20 mm Hg achieved in our study is low but clinically representative of PP achieved using a noninvasive pulsator with a hollow-fiber membrane oxygenator. Additionally, PP amplitude itself may not be a primary factor. In several studies, mean PP values of 30 and 34 mm Hg did not improve renal function (7,8), whereas in other studies, PP values of 25, 30, and 36 mm Hg were reported as beneficial (5,6,9). What may be of more importance is the actual rate of rise of pressure, or dP/dt, which can be partially implied from the contour of the arterial pressure waveform. At least some of the purported benefits of pulsatile perfusion appear to be associated with the increased kinetic energy that results from a higher dP/dt (17). In our pulsatile perfusion group, dP/dt was probably low, because the arterial waveform during CPB was generally more sinusoidal in appearance compared with that generated by the normal heart, as shown in Figure 7. Finally, the pump flow rate to which pulsatile perfusion is added may be important. A recent study in dogs undergoing normothermic CPB found increased renal blood flow and decreased renal lactate production with a PP of 40 mm Hg when flows were 80 and 100 $mL \cdot kg^{-1} \cdot min^{-2}$ (1.7 and 2.1 $mL \cdot min^{-1} \cdot m^{-2}$) but not at flows of 40, 60, or 120 $mL \cdot kg^{-1} \cdot min^{-2}$ (1.0, 1.3, and 2.4 $mL \cdot min^{-1} \cdot m^{-2}$) (18). Because our patients received pump flows of 2.0–2.5 $mL \cdot min^{-1} \cdot m^{-2}$, they may have received too high a flow to show the maximal benefit.

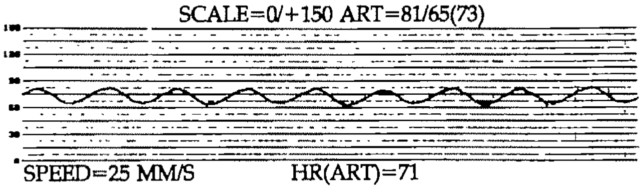

Figure 7. Sample tracing of arterial (ART) blood pressure (mm Hg) during pulsatile cardiopulmonary bypass. Note slow upstroke and almost sinusoidal appearance. HR, heart rate (beats/min).

The variables that we measured are not as sensitive markers of renal function as are inulin or creatinine clearance, both of which measure glomerular filtration rate. However, the latter measurements require at least 1 h of steady-state conditions for each determination (19). Because the cross-clamp time and resultant pulsatile period was less than 1 h, these steady-state conditions would not have been achieved. Urine output, although a crude measure of renal function, is the most routinely used clinical variable. Our results, showing an increase in U/O during CPB in all groups, have been observed elsewhere and are thought to be due to the hemodilution that these patients experience (20). Measures such as fractional excretion of sodium and potassium and RFI, which assess renal tubular function, have been used by others (10,21,22). A similar rise in these variables during and after CPB was also noted in these studies and was believed to reflect clearance of the increased solute load that CAB patients receive (21).

Our inability to clearly show better preservation of renal function with any of the treatment options may have been because these parameters do not in fact influence renal function. It may also have occurred because the majority of patients that we studied had normal preoperative renal function. Two studies have recently shown that preoperative renal insufficiency and postoperative circulatory dysfunction are the best predictors of postoperative renal failure, as opposed to circulatory variables obtained during CPB (23,24). The fact that all three of our patients who developed ARI postoperatively were hemodynamically unstable, requiring vasopressors and intraaortic balloon counterpulsation, supports this observation.

In summary, using a randomized, prospective study design, we were unable to show any clinically relevant differences in intraoperative or postoperative renal function when comparing pulsatile/nonpulsatile perfusion simultaneously with α-stat/

pH-stat management during hypothermic CPB in CAB patients with normal preoperative renal function.

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Effects of Sodium L-Lactate and Sodium Racemic Lactate on Intraoperative Acid-Base Status

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Lactated Ringer's solution is frequently used to avoid metabolic acidosis during fluid resuscitation. The standard lactated Ringer's solution contains racemic lactate, an equal mixture of the D- and L-stereoisomers. We investigated whether sodium L-lactate or sodium racemic lactate (DL-lactate) is more effective for increasing buffering capacity in body fluids. For the purpose of this comparison, Ringer's solutions containing no lactate, sodium L-lactate, or racemic lactate at a concentration of 84 mEq/L (three times more than the ordinary level) were infused in patients under general anesthesia during tympanoplasty. Although differences occurred among the three groups in blood concentrations of L-lactate, D-lactate, and the L-lactate/pyruvate ratio, no differences occurred between the two lactate groups in either bicarbonate ion concentration or base excess. The amount of buffering capacity increased significantly in both lactate groups, compared with preinfusion levels, and was more than the values in the nonlactated Ringer's solution group. We conclude that sodium racemic lactate is metabolized at nearly the same rate as that of sodium L-lactate.

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There are two stereoisomers of lactate. The physiologic lactate produced by cellular metabolism is L-lactate, and D-lactate is normally present in only trace concentrations in vivo (1). It has been proposed that the metabolic rate and utilization of D-lactate are inferior to those of L-lactate (2,3). Lactated Ringer's solution containing racemic lactate is commonly used as an intraoperative fluid for several reasons. Lactated Ringer's solution has an electrolyte composition similar to that of extracellular fluids, except that lactate replaces bicarbonate. Metabolism of sodium lactate produces an equimolar sodium bicarbonate that is intimately involved with maintenance of the acid-base balance (4). Since Hartmann and Senn (5) introduced lactated Ringer's solution in the 1930s, it has been a racemic mixture of equal amounts of L- and D-lactate. Lactated Ringer's solution containing only L-lactate is now commercially available in Japan. There are no data on the relative rates of metabolism of D- and L-lactate in humans. The purpose of this study was to determine whether or not there is any difference between sodium L-lactate and sodium racemic lactate with regard to their rate of conversion to bicarbonate.

Methods

This study was approved by the Institutional Review Board in our hospital, and consent was obtained from each patient at the time of a preanesthetic visit. Forty adult patients undergoing tympanoplasty under general anesthesia were assigned randomly to three groups by drawing envelopes: a nonlactate group ($n = 10$), an L-lactate group ($n = 15$), and a DL-lactate group ($n = 15$) (Table 1). Subjects with liver or renal disease or metabolic disorders such as diabetes were excluded from the study.

The nonlactate group received plain Ringer's solution (Otsuka Pharmaceutical Co., Ltd.) without lactate. Standard lactated Ringer's solution contains 28 mEq/L of DL-lactate; however, in the L-lactate and DL-lactate groups, we used sodium lactate at a concentration of 84 mEq/L, three times higher than usual (Table 1). In the L-lactate group, a lactated Ringer's solution containing 84 mEq/L of only L-lactate was prepared by adding sodium L-lactate (1 M solution, Shimizu Pharmaceutical Co., Ltd.) to L-lactated Ring-

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Table 1. Chemical Composition of Plain Ringer's Solution and Two High-Concentrate Lactated Ringer's Solutions Used in the Three Study Groups

	Na	K	Ca	Cl	L-Lactate	D-Lactate
Plain Ringer's solution (nonlactate group)	147	4	4.5	155.5		
L-Lactated Ringer's solution (L-lactate group)	186	4	3	109	84	
DL-Lactated Ringer's solution (DL-lactate group)	186	4	3	109	42	42

Values are expressed as milliequivalents per liter.

er's solution (Solita, Shimizu Pharmaceutical). In the DL-lactate group, lactated Ringer's solution containing 42 mEq/L of sodium L-lactate and 42 mEq/L of sodium D-lactate was prepared by adding calculated amounts of DL-lactate (1 M solution, Otsuka Pharmaceutical) to DL-lactated Ringer's solution (Lactec, Otsuka Pharmaceutical).

After intravenous cannulation, normal saline solution (0.9% NaCl) was administered in all patients at a rate of 5 $mL \cdot kg^{-1} \cdot h^{-1}$. Anesthesia was induced with droperidol, fentanyl, thiopental, and succinylcholine chloride and maintained with a neuroleptic anesthesia technique (droperidol/fentanyl/nitrous oxide/oxygen). Pancuronium was used for neuromuscular blockade. Controlled mechanical ventilation was adjusted to maintain $Paco_2$ between 35 and 40 mm Hg, and rectal temperature was maintained between 36 and 37°C. Radial artery cannulation was used for serial blood sampling, and an indwelling urethral catheter was inserted to collect urine. After the collection of blood for baseline values (0 min), one of the three Ringer's solutions was infused at a rate of 500 mL for an initial 20 min, followed by 5 $mL \cdot kg^{-1} \cdot h^{-1}$ for a subsequent 3 h and 10 min. Blood samples were obtained at 30 min and 1, 1.5, 2.5, and 3.5 h after the initiation of infusion. All studies were completed before the end of surgery.

Measurement of pHa, $Paco_2$, HCO_3^-, and base excess was performed with an ABL-2 blood gas analyzer (Radiometer Co.). L-Lactate, D-lactate, and pyruvate were measured by enzymatic analysis and spectrophotometry. Measurement of D-lactate was based on the method previously described by Brandt et al. (1). Because L-lactate and pyruvate values may change over time during serum separation after blood collection (6), blood was deproteinized immediately after sampling with 1.5 M cooled perchloric acid and then centrifuged. The supernatant was used for the determination process. The values reported are for the whole-blood concentration. Blood glucose was measured enzymatically with a glucose analyzer (YSI Co.).

The values obtained are expressed as mean ± SD. A significant difference within groups was tested first by using the repeated-measures analysis of variance, and where indicated, the paired t-test was used to identify significant differences from the baseline value. Significant differences among groups were tested first by analysis of variance and, if indicated, were determined between two groups by using the Bonferroni modification of the t-test, as previously described (7,8). A value of $P < 0.05$ was considered significant.

Table 2. Clinical Characteristics of 40 Adult Patients Undergoing Tympanoplasty Under General Anesthesia

	Nonlactate group (n = 10)	L-Lactate group (n = 15)	DL-Lactate group (n = 15)
Gender (M/F)	5/5	9/6	8/7
Age (yr)	43.2 ± 12.1	41.3 ± 18.2	50.1 ± 18.3
Weight (kg)	58.1 ± 13.8	56.4 ± 8.9	54.5 ± 8.2
Height (cm)	161.1 ± 10.9	157.8 ± 8.1	155.3 ± 7.1
Hemoglobin (g/dL)[a]	14.2 ± 1.6	13.6 ± 2.2	13.6 ± 2.0
Epinephrine (mL)[b]	9.1 ± 2.5	9.2 ± 3.0	8.5 ± 2.8
Bleeding (mL)	25.0 ± 14.1	35.0 ± 25.5	28.0 ± 18.2
Duration of operation (h)	4.46 ± 0.78	4.99 ± 1.07	4.11 ± 0.89

M, male; F, female.

Values are expressed as mean ± SD or number of patients. There were no statistically significant differences between groups.

[a] Preoperative hemoglobin.

[b] Total volume of epinephrine (1:100,000) applied to operative fields during surgery.

Results

The three groups were similar in terms of gender, age, body weight, height, preoperative hemoglobin concentration, the time of starting anesthesia, doses of epinephrine applied to the operative field, and the volume of blood loss (Table 2).

Arterial blood gas data are presented in Figure 1. Arterial pH increased in both the L- and DL-lactate groups but not the nonlactate group. At all time points after 1 h, the values in both the L- and DL-lactate groups were significantly higher than those in the nonlactate group, and there were no significant differences between the L- and DL-lactate groups. Among groups, there were no significant differences

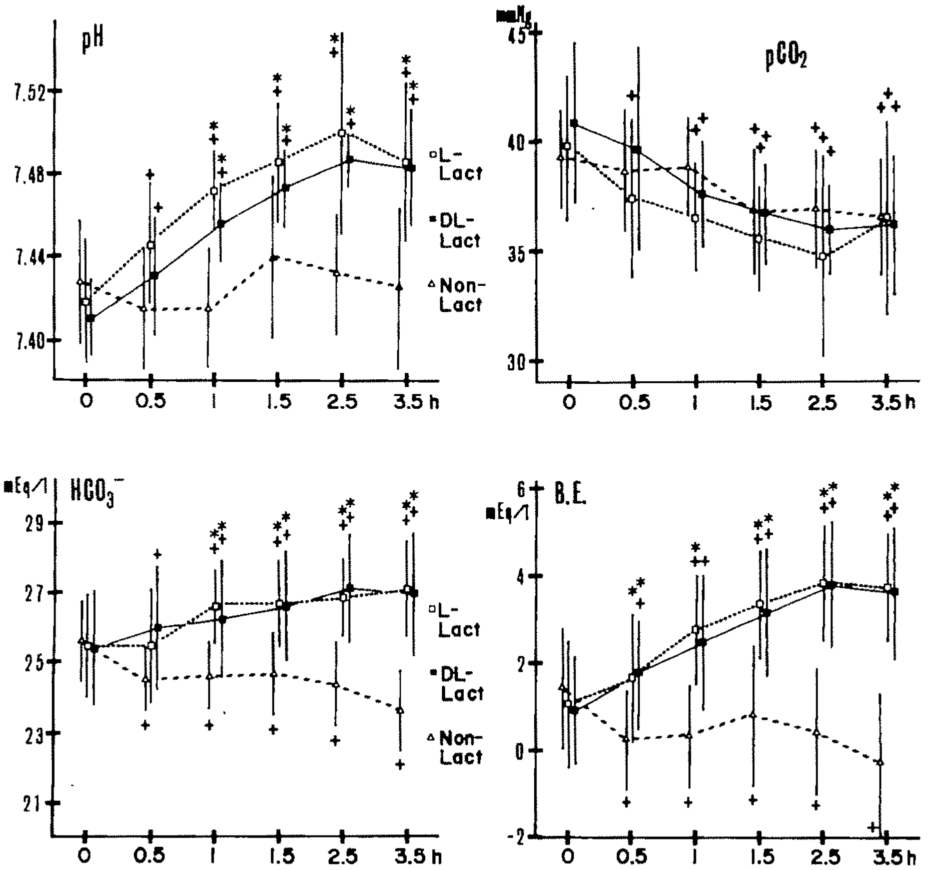

Figure 1. Effects of infusions of nonlactated (Non-Lact), L-lactated (L-Lact), or DL-lactated (DL-Lact) Ringer's solution on arterial blood gas tensions (mean ± SD). †Significant differences from 0-h (baseline) value among groups ($P < 0.05$). *Significant differences versus nonlactate group ($P < 0.05$). There was no significant difference between L-lactate and DL-lactate groups. B.E., base excess.

at any time in $Paco_2$, which was slightly decreased from baseline value. Both bicarbonate concentration and base excess values increased in the L- and DL-lactate groups but decreased in the nonlactate group. There were no differences between the L- and DL-lactate groups.

In the L-lactate group, the concentration of L-lactate in blood increased from 8.1 mg/dL (0.90 mEq/L) at baseline to 19.2 mg/dL (2.13 mEq/L) after 30 min, significantly higher than in the nonlactate and DL-lactate groups (Figure 2). Conversely, in the DL-lactate group, the D-lactate concentration increased from 0.24 mg/dL (0.03 mEq/L) at baseline to 6.06 mg/dL (0.67 mEq/L) after 30 min, significantly greater than that in the nonlactate and L-lactate groups. No difference was noted between the L- and DL-lactate groups in the concentration of pyruvate in blood, which increased from baseline value in both groups and was significantly greater than that in the nonlactate group at 30 min, 1 h, and 1.5 h (Table 3). The ratio of L-lactate to pyruvate (L/P ratio) was higher in the L-lactate group than in the DL-lactate or nonlactate group 30 min after administration. However, no difference was noted between the L- and DL-lactate groups in the ratio of (L-lactate + D-lactate) to pyruvate. There were no differences among groups in blood glucose (Table 3).

Excretion of L-lactate in urine during the entire study period was scarcely observed in the nonlactate group (mean 0.07 mmol) and was slight in both the L- and DL-lactate groups (0.25 and 0.19 mmol, respectively), showing <0.3% of the amount administered in 3.5 h. Slight excretion of D-lactate was also noted in the L-lactate group (0.02 mmol) but was significantly greater in the DL-lactate group (0.94 mmol), although the amount excreted in the DL-lactate group was only 1.5% of the amount administered.

No differences were noted among groups in urinary output, pulse rate, blood pressure, arterial oxygen tension, and arterial oxygen saturation. Awakening from anesthesia was smooth and uneventful in each patient. No impairment in cerebral function, such as agitation, confusion, and panic attacks, was observed postoperatively.

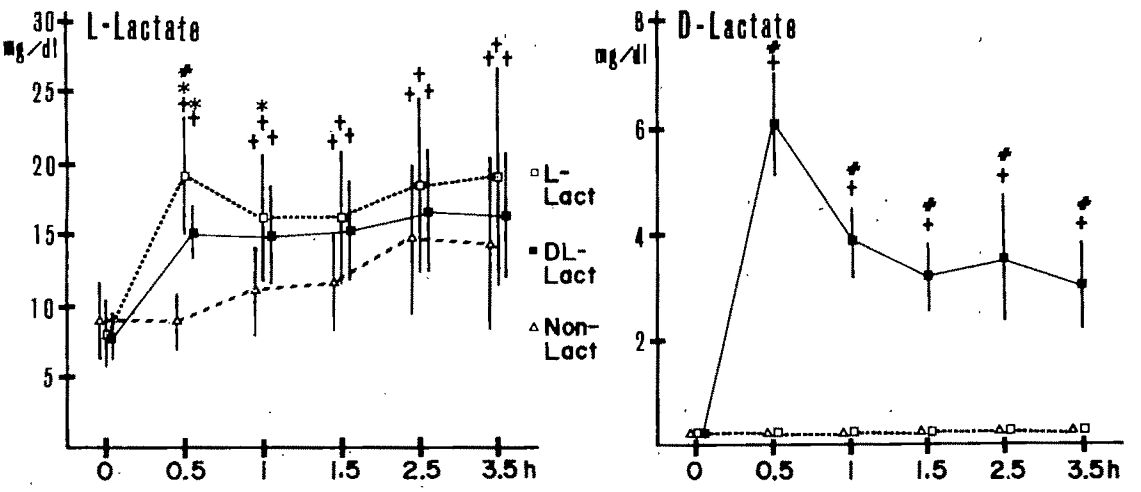

Figure 2. Blood L-lactate and D-lactate concentrations (mean ± SD) in the three study groups. †Significant differences from 0-h (baseline) value among groups ($P < 0.05$). *Significant differences versus nonlactate (Non-Lact) group ($P < 0.05$). ‡Significant differences between L-lactate (L-Lact) and DL-lactate (DL-Lact) groups ($P < 0.05$).

Discussion

The utilization of lactate for oxidation or gluconeogenesis either uses hydrogen or generates bicarbonate (9). Therefore, 1 mol of sodium lactate produces 1 mol of sodium bicarbonate, according to the following formulas:

Oxidation:

$$\begin{aligned} &CH_3CH(OH)COO^-Na^+ + HOH + 3\,O_2 \\ &\rightarrow Na^+ + OH^- + 3\,CO_2 + 3\,H_2O \\ &\rightarrow NaHCO_3 + 2\,CO_2 + 3\,H_2O \end{aligned} \qquad (1)$$

Gluconeogenesis:

$$\begin{aligned} &2\,CH_3CH(OH)COO^-Na^+ + 2\,H_2O + 2\,CO_2 \\ &\rightarrow C_6H_{12}O_6 + 2\,NaHCO_3. \end{aligned} \qquad (2)$$

Alpert and Root (3) reported that 10 min was required for 40% metabolism of the dosed amount of L-lactate in dogs. The calculated lactate utilization rate in humans was estimated to be approximately 200 mmol/h by Kreisberg (10). Therefore, bicarbonate is rapidly produced from lactate so that the concentration of bicarbonate at 30 min in the L-lactate group in our study was significantly higher than that of the nonlactate group.

Equations (1) and (2) were based on L-lactate but may be applied to D-lactate. D-Lactate was formerly considered to be transformed to L-lactate by lactate racemase or metabolized to pyruvate by D-lactate dehydrogenase, enzymes that are found in microorganisms. However, it is currently believed that D-lactate is metabolized to pyruvate in mammals by a nonspecific enzyme of D-2-hydroxy acid dehydrogenase (11,12). The metabolism after pyruvate remains the same as for L-lactate, although the proportion of oxidation to gluconeogenesis may be different between D- and L-lactate (13). Accordingly, the alkalinizing effects of both sodium lactates should depend on their metabolic rates.

It is commonly believed that the metabolism of D-lactate is slower than that of L-lactate and that D-lactate is poorly utilized in vivo. These views are derived from early studies. In 1929, Cori and Cori (2) reported that D-lactate was utilized four times more slowly than L-lactate and that 30% of the amount of D-lactate that was absorbed was excreted in the urine, whereas no excretion of L-lactate occurred during L-lactate absorption. Furthermore, Alpert and Root (3) reported that L-lactate required 10 min for 40% metabolism of the dosed amount in dogs, whereas the racemic form required 23 min. Therefore, based on the supposition that lactated Ringer's solution consisting of sodium L-lactate must be superior to the racemic form in its capacity to produce available buffer, a Japanese pharmaceutical company developed a lactated Ringer's solution consisting of sodium L-lactate, which has been available since 1982.

In the current study, the concentration of sodium lactate was made three times higher than the standard lactated Ringer's solution, and doses of 42 mEq of lactate were infused for an initial 20 min followed by 0.42 $mEq \cdot kg^{-1} \cdot h^{-1}$ for a subsequent 3 h and 10 min to allow us to detect differences among solutions. The rate of lactate administration of 0.42 $mEq \cdot kg^{-1} \cdot h^{-1}$ is equivalent to 15 $mL \cdot kg^{-1} \cdot h^{-1}$ of standard lactated Ringer's solution. No difference,

Table 3. Pyruvate, Lactate/Pyruvate Ratio, and Glucose Levels in Blood Before and After Start of Infusion

	Baseline value	After start of infusion				
		0.5 h	1 h	1.5 h	2.5 h	3.5 h
Pyruvate in blood (mg/dL)						
Non	0.83 ± 0.27	0.87 ± 0.31	0.89 ± 0.28	1.05 ± 0.36^{a}	1.22 ± 0.42^{a}	1.16 ± 0.51
L-L	0.91 ± 0.35	1.49 ± 0.36^{a,b}	1.38 ± 0.41^{a,b}	1.47 ± 0.43^{a}	1.48 ± 0.49^{a}	1.39 ± 0.48^{a}
DL-L	0.84 ± 0.34	1.43 ± 0.31^{a,b}	1.40 ± 0.43^{a,b}	1.46 ± 0.47^{a}	1.53 ± 0.51^{a}	1.39 ± 0.49^{a}
L-Lactate/pyruvate ratio						
Non	10.3 ± 1.2	10.5 ± 2.4	12.7 ± 2.2^{a}	11.2 ± 1.3	12.2 ± 2.4	12.6 ± 1.7^{a}
L-L	9.5 ± 1.9	13.3 ± 2.5^{a-c}	12.1 ± 2.6^{a}	11.3 ± 2.0^{a}	12.7 ± 2.2^{a}	14.0 ± 3.2^{a}
DL-L	9.9 ± 2.8	10.8 ± 1.9	11.1 ± 2.6	11.1 ± 3.2	11.6 ± 3.3	12.4 ± 3.3^{a}
(L-Lactate + D-lactate)/pyruvate ratio						
Non	10.6 ± 1.2	10.7 ± 2.5	13.0 ± 2.2^{a}	11.5 ± 1.3	12.5 ± 2.4	12.8 ± 1.7^{a}
L-L	9.7 ± 1.9	13.5 ± 2.5^{a}	12.3 ± 2.6^{a}	11.5 ± 2.0^{a}	12.9 ± 2.3^{a}	14.2 ± 3.2^{a}
DL-L	10.3 ± 2.9	15.3 ± 3.0^{a,b}	14.0 ± 3.4^{a}	13.4 ± 3.9^{a}	14.0 ± 3.8^{a}	14.8 ± 3.7^{a}
Glucose in blood (mg/dL)						
Non	87.7 ± 8.0	85.8 ± 11.1	94.1 ± 12.2	89.8 ± 8.0	93.1 ± 13.8	93.4 ± 12.5
L-L	88.5 ± 14.9	94.6 ± 25.2	99.0 ± 26.8^{a}	98.5 ± 35.2	99.1 ± 36.0	95.3 ± 23.0^{a}
DL-L	85.1 ± 9.6	84.8 ± 10.6	94.9 ± 16.2^{a}	90.9 ± 15.9^{a}	84.1 ± 11.3	87.7 ± 12.6

Non, nonlactate group; L-L, L-lactate group; DL-L, DL-lactate group.
Values are expressed as mean ± SD.
[a] Significant difference from baseline value among groups ($P < 0.05$).
[b] Significant difference versus nonlactate group ($P < 0.05$).
[c] Significant difference between L-lactate and DL-lactate groups ($P < 0.05$).

however, was noted between the L-lactate and racemic lactate groups as to the alkalinizing effect. Therefore, at the dose level used in this study, the metabolic rate of racemic lactate is the same as that of L-lactate.

Normal L-lactate concentration in blood is approximately 9 mg/dL (1 mEq/L). The highest concentration of L-lactate attained was 41.3 mg/dL (4.5 mEq/L) in a patient in the L-lactate group 3.5 h after the start of infusion. L-Lactic acidosis is defined as >5–6 mEq/L for L-lactate and <7.35 for pH (14). L-Lactate concentrations of 2–5 mEq/L represent a "gray area" of clinical significance and were seen in association with mild exercise or hypermetabolic disease (14).

Normal D-lactate concentration in blood is 0.21 mg/dL (0.023 mEq/L) (1). The highest concentration of D-lactate attained was 7.54 mg/dL (0.84 mEq/L) in a patient in the D-lactate group at 30 min after infusion. Elevation of blood D-lactate to >3 mEq/L has been associated with impaired cerebral function in patients and in experimental animals (15). The data obtained with D-lactate in our experiment were always below this level and were not associated with any side effects.

Both L- and D-lactate are metabolized predominantly in the liver and partially in the kidney and muscles, although their metabolic and utilization rates are different (4,16). Our study, however, was performed in patients with normal liver function. Further studies are required in patients with hepatic dysfunction.

The ratio of L-lactate to pyruvate (L/P ratio) has been used as a quantitative index of oxygen deficiency in the tissues and of the redox state in cytosol (17). At present, however, this ratio has not been considered useful because of problems that include difficulty in measuring pyruvate clinically (14). Because pyruvate is unstable once the sample is drawn, any lag time in processing the specimen can result in a lower value and an increased L/P ratio (4,6). Furthermore, the lack of in vivo equilibrium conditions when oxidation-reduction relations are determined is also problematic (14,18). The L/P ratio in this study indicated significantly higher values in the L-lactate group 30 min after administration than those in the DL-lactate group. However, whether a greater level of hypoxia or intracellular oxygen deficiency was caused by the administration of L-lactate compared with racemic lactate was not considered. It may simply be caused by the administration of doses of L-lactate in the L-lactate group that were two times larger than in the DL-lactate group. Accordingly, it is necessary in general to consider the reason why the L/P ratio was enhanced and to check the presence of lactate supplied extrasomatically, as indicated in this study, before presuming the hypoxic state in tissues. On the other hand, the L/P ratio on addition of D-lactate (i.e., [L-lactate + D-lactate]/pyruvate ratio) showed no difference between the L- and DL-lactate groups. If the metabolic rate from D-lactate to pyruvate is slower than that from L-lactate to pyruvate, then the ratio is considered to show the higher value in the DL-lactate group compared with that in the L-lactate group. From this result, too, the metabolic rate of racemic lactate must be nearly the same as that of L-lactate.

Lactate is a precursor of liver glycogen (2); therefore infusion of lactated Ringer's solution in diabetic patients may produce hyperglycemia (19). In this study, lactate was infused at a concentration three times higher than normal, but only small increases in blood glucose were observed.

Excretion of D-lactate in urine occurred in all groups, whereas L-lactate was minimally excreted in urine. Judge and van Eys (20) observed that normal humans excreted the nonphysiologic isomer of D-lactic acid and speculated about a difference in the renal threshold of L- and D-lactate (12). The total amount of D-lactate excreted over 3.5 h was larger in the DL-lactate group than in the L-lactate group but was only 1.5% of the dose infused. This corresponds to approximately one-twentieth of 30%, the value that was estimated by Cori and Cori (2). They administered racemic lactate at doses of 10–20 mmol/kg, more than 10 times larger than in our study. Therefore D-lactate in our study doses was presumed to be sufficiently utilized in vivo. Our results are in agreement with the report by Drury and Wick (16) that racemic lactate is completely metabolized in vivo in rabbits. Furthermore, Coran (21) reported that on administration of 1 L of racemic lactated Ringer's solution in baboons over 30 min, D-lactate steadily disappeared from the blood in a little longer time than that observed with L-lactate. However, there has as yet been no report with respect to humans.

In conclusion, sodium racemic lactate is metabolized at nearly the same rate as that of sodium L-lactate by infusion doses of 42 mEq for an initial 20 min, followed by $0.42\ \mathrm{mEq \cdot kg^{-1} \cdot h^{-1}}$ for a subsequent 3 h and 10 min of general anesthesia in patients without liver or renal dysfunction.

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A Comparison of the Effects of Propofol and Nitrous Oxide on the Electroencephalogram in Epileptic Patients During Conscious Sedation for Dental Procedures

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The influence of sedative doses of propofol or nitrous oxide on the electroencephalogram was studied in 11 mentally handicapped patients with treated epilepsy undergoing dental procedures. At one session, propofol was titrated to achieve conscious sedation. The mean (±SD) dose requirements were $5.5 \pm 1.1\ mg \cdot kg^{-1} \cdot h^{-1}$. In six patients, the electroencephalogram was unchanged during propofol administration. In three patients, there was a decrease in epileptic activity, and in two patients, paroxysmal discharges disappeared. At another session, nitrous oxide was administered by nasal mask. The mean (±SD) concentration of nitrous oxide needed was 43.6% ± 4.8%. The electroencephalogram did not change in nine patients, whereas in two patients epileptic activity decreased. There were no clinical epileptoid or other adverse manifestations during any treatment or up to 48 h thereafter. The results of the present study suggest that propofol or nitrous oxide can be administered in subanesthetic doses for conscious sedation in mentally handicapped patients with treated epilepsy.

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Propofol is the latest intravenous anesthetic to be introduced into clinical practice. It has been used for sedation in subanesthetic doses for short periods to supplement regional anesthesia (1,2) and for longer periods in patients in intensive care units (3,4). Discontinuation of propofol infusion results in rapid recovery because of its favorable pharmacokinetic profile (5). In a previous study, we administered propofol by continuous infusion for conscious sedation in mentally and physically handicapped patients undergoing dental procedures in whom nitrous oxide sedation had failed or was not possible to administer (6). However, there are conflicting data with respect to the proconvulsive or anticonvulsive properties of propofol (7–17). Because epilepsy is a common additional disorder in the handicapped patient, it is important to know whether intravenous sedation with propofol might provoke seizures or enhance interictal electroencephalographic (EEG) manifestations. The present study was designed to investigate the effects of propofol and nitrous oxide, titrated to achieve conscious sedation, on the EEG in epileptic patients undergoing dental procedures.

Methods

Eleven mentally handicapped patients with epilepsy who required dental treatment under sedation were prospectively studied. Pregnant patients and patients with a history of allergy to propofol or its vehicle were excluded from the study. Written, informed consent was obtained from the parents of the patients, and the study protocol was approved by the institutional ethics committee. A medical history was obtained from all patients. Weight, height, and arterial blood pressure were measured, and a physical examination was carried out. All preoperative medication was recorded and continued up to the time of the procedure.

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All patients were known to have primary or secondary epilepsy. The diagnosis of epilepsy was based on the presence of clinical seizures and confirmed by EEG demonstration of seizure activity. Epilepsy was adequately controlled with medication in all patients. Patients were randomly assigned to receive either propofol or nitrous oxide/oxygen for their first treatment and the alternative sedative regimen for the second treatment. Each patient was thus studied twice on different days. Patients for the morning sessions fasted; patients who were treated in the afternoon were allowed a light breakfast. No premedication was administered.

At each session, the initial procedures were performed without sedation. These involved explanation, adaptation to the surroundings, and oral examination where possible (step 1). Then either propofol or nitrous oxide sedation was introduced, and the following dental procedures were performed: removal of calculus and taking intraoral radiographs if indicated (step 2). The next stage included sealing of fissures, cavity preparation, and restoration and extraction if necessary (step 3). If the patient did not tolerate procedures during step 1, sedation was started. Articaine HCl was administered for local analgesia if necessary. The same dental surgeon performed the treatment in all patients.

The EEG was continuously monitored and recorded with a 12-channel Siemens-Elema recorder at a paper speed of 3 cm/s and with a time constant of 0.3, 0.6, or 1.2 s, according to the degree of restlessness of the patient. The gain was 70 or 100 μV/cm. The scalp electrodes were placed at F_{p1}, F_{p2}, T_3, T_4, C_3, C_4, O_1, and O_2 (International 10-20 System). The electrode impedance was ≤ 5 kΩ. A bipolar montage was used. All events and changes of dosages were manually marked, with indication of the time.

The EEG was recorded continuously throughout the dental procedure, starting with a 5-min baseline recording. The EEG recordings were continued for 15 min after discontinuation of sedation. The EEG was visually assessed for epileptic activity by a clinical neurophysiologist who was unaware of the sedative regimen used. Spikes, spike waves, and sharp waves with local or diffuse distribution were considered epileptic discharges.

A continuous infusion of propofol was started at an initial rate of 3.5 $\mathrm{mg \cdot kg^{-1} \cdot h^{-1}}$ via a Braun Secura FT syringe pump (B. Braun, Melsungen AG, Germany), and a loading dose of propofol (0.5–1 mg/kg) was administered by slow intravenous injection until sedation score 3 was reached (Table 1). Thereafter, the infusion rate was adjusted as necessary to maintain sedation score 3, avoiding unconsciousness (sedation score 5).

Nitrous oxide sedation was administered by the dental surgeon with the Porter MXR machine (Porter Instrument Co., Heatfield, Pa.) equipped with a Dameca scavenging system (Dameca, Copenhagen, Denmark) and a nasal mask (Dameca). The initial nitrous oxide concentration was 40% in oxygen. Nitrous oxide was administered and titrated to the same clinical endpoints of sedation as propofol (sedation score 3).

Table 1. Sedation Scores

1	Fully awake and oriented
2	Drowsy
3	Eyes closed, responds promptly to verbal commands
4	Eyes closed, arousable on mild physical stimulation
5	Eyes closed, unarousable on mild physical stimulation

In addition to EEG monitoring, the level of consciousness was constantly assessed using the sedation score. Continuous verbal and nonverbal communication with the patient was maintained. Nonverbal communication was maintained with those patients for whom verbal communication was difficult or impossible. Their hands were squeezed to assess their response. Any excitatory effects, such as spontaneous movements, twitching, or tremor, were noted. Electrocardiogram, heart rate, noninvasive arterial blood pressure, pulse oximetry ($\mathrm{Spo_2}$), and end-tidal carbon dioxide concentration ($\mathrm{P_{ET}CO_2}$) were continuously monitored using Hewlett Packard 78352A (Böblingen, Germany) and Ohmeda 4700 Oxicap (Englewood, Colo.) monitors. Ten minutes after the dental procedure was completed, the patients returned to their ward. The patients were observed by their personal attendants during the whole procedure and until 48 h after sedation for any side effects and complications.

The possibility of determining propofol blood concentration became available only at the end of the study. Therefore, propofol concentration was measured in the last three patients. Blood samples of 5 mL were obtained from the contralateral antecubital vein on ending the propofol infusion. Samples were collected in tubes containing potassium oxalate and stored at 4°C until assay of blood concentration of propofol by the combination of high-pressure liquid chromatography and fluorescence detection method (18).

A repeated measures analysis of variance was performed for each physiologic variable (arterial blood pressure, heart rate, oxygen saturation [$\mathrm{Spo_2}$], and $\mathrm{P_{ET}CO_2}$) using the statistical package BMDP (BMDP Statistical Software, Berkeley, Calif.). Differences between time trends in both sedation groups were tested. Results are expressed as mean ± SD. A value of $P < 0.05$ was considered to be statistically significant.

Table 2. Clinical Characteristics of Eleven Mentally Handicapped Patients With Epilepsy Undergoing Dental Treatment Under Sedation

Pt No./ Gender	Age (yr)	Wt (kg)	Diagnosis	Previous EEG	Medication	Epileptic attacks
1/M	25	43	Mental retardation, epilepsy	Focal ep act	Carbamazepine; valproic acid	1 Seizure in 7 mo
2/M	24	59	Mental retardation, epilepsy	Multifocal ep act	Carbamazepine	Seizure free
3/F	25	52	Mental retardation, epilepsy, deaf	Focal and generalized ep act	Valproic acid; carbamazepine	Twice a day
4/F	18	59	Mental retardation, epilepsy, spastic tetraparesis	Generalized ep act during HV	Valproic acid; diazepam	Once a day
5/F	19	41	Mental retardation, epilepsy, spastic tetraparesis	Multifocal and generalized ep act	Valproic acid	Seizure free
6/M	17	57	Mental retardation, epilepsy, spastic tetraparesis	Diffuse slow frequencies without ep act	Valproic acid; carbamazepine	1–2 Petit mal/wk; 1 seizure in 6 mo
7/M	30	105	Mental retardation, epilepsy	Generalized ep act during HV	Valproic acid	2–3 Seizures in 2 wk
8/F	21	40	Mental retardation, epilepsy, spastic tetraparesis, blind	Multifocal and generalized ep act	Carbamazepine	3 Seizures in 1 wk
9/F	18	40	Mental retardation, epilepsy, hydrocephalus	Normal	Phenobarbital; valproic acid	Seizure free
10/F	26	52	Mental retardation, epilepsy, spastic tetraparesis	Multifocal ep act	Carbamazepine; phenobarbital	Once a day
11/F	19	48	Tuberous sclerosis, mental retardation, epilepsy	Focal and generalized ep act	Phenytoin; carbamazepine	1 Petit mal/day; 1 seizure/day

Pt, patient; EEG, electroencephalogram; M, male; F, female; ep act, epileptic activity; HV, hyperventilation.

Table 3. Electroencephalographic Data Before and During Sedation in the Eleven Study Patients

		EEG data				
		Before sedation				
Pt No.	Drug[a]	Normal	Diffuse slow	Focal	Paroxysmal discharge[b]	During sedation
1	N (45%)		×		3 in 15 min	9 Paroxysmal discharges in 68 min
	P (5)		×		11 in 16 min	None
2	N (40%)	×			Some sharp waves	No change
	P (4.4)	×			Some sharp waves	No change
3	N (50%)		×	×	Spikes, spike waves	No change
	P (4.8)		×	×	Spikes, spike waves	No change
4	N (40%)	×				No change
	P (6.4)	×				No change
5	N (40%)	×		×	Spikes 1–3/10 s	No change
	P (5.7)	×		×	Spikes 1–3/10 s	No change
6	N (40%)		×	×	Rare sharp waves	No change
	P (5.4)		×	×		No change
7	N (45%)	×				No change
	P (3.7)	×			14 in 19 min	None
8	N (35%)		×	×	Some spikes	No change
	P (4.4)		×	×	Some spikes	Decrease of spikes
9	N (45%)	×			Some sharp waves	No change
	P (7.3)	×			Some sharp waves	No change
10	N (50%)		×		Some sharp waves	No change
	P (6.6)		×		Some sharp waves	Decrease of sharp waves
11	N (50%)		×	×	25 in 15 min	22 Paroxysmal discharges in 35 min 22 in 5 min postsedation
	P (6.5)		×	×	75 in 24 min	13 Paroxysmal discharges in 50 min 50 in 15 min postsedation

EEG, electroencephalographic; N, nitrous oxide; P, propofol; Pt, patient.

[a] Numbers in parentheses are nitrous oxide concentrations (%) or propofol dose (bolus dose + total cumulative dose) (mg·kg^{-1}·h^{-1}).

[b] Epileptic activity including spikes, spike waves, and sharp waves.

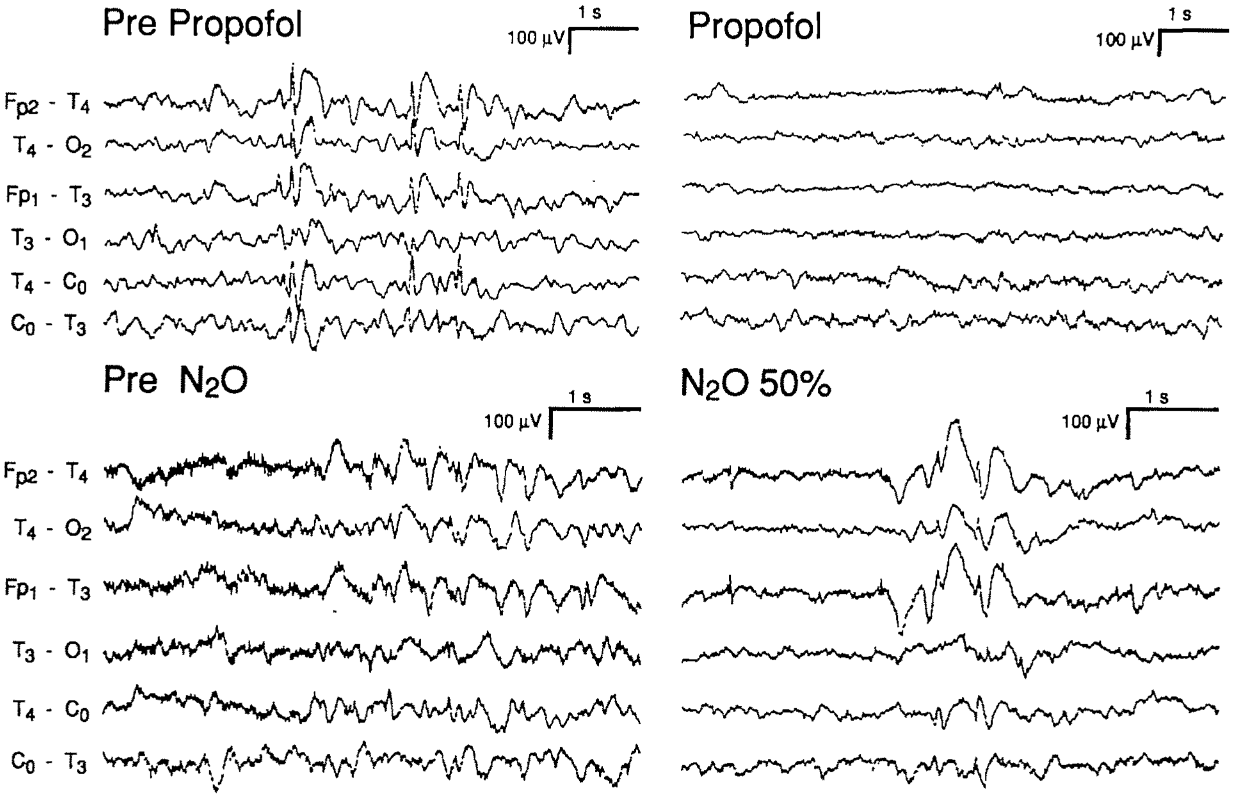

Figure 1. Representative EEG segments from a 19-yr-old patient (patient 11) with treated epilepsy before and during conscious sedation with propofol and nitrous oxide. Note absence of spike-and-wave complexes during propofol sedation.

Results

Demographic and clinical details of the patients (7 women, 4 men) are shown in Table 2. Eight of the 11 patients had multiple handicaps. Five patients were severely mentally retarded, two were moderately retarded, and four were mildly retarded. Apart from their mental disorder and physical handicap, all patients were in good health. All but one patient (patient 9) had EEG evidence of epileptic activity.

The EEG activity data before and during sedation are shown in Table 3. During propofol sedation, EEG activity did not change in six patients. Paroxysmal discharges disappeared in two patients (patients 1 and 7) and were decreased in three (patients 8, 10, and 11) (Figure 1). In three patients (patients 4, 6, and 8), there was an increase in fast activity in the beta band (13–30 Hz). During nitrous oxide sedation, the EEG did not change in nine patients. In two patients (patients 1 and 11), a decrease in epileptic activity was evident. Neither form of sedation was associated with any adverse effects. Specifically, there was no increase in the frequency or intensity of clinical epileptic manifestations during the 48 h after treatment.

The mean duration of sedation was 40.0 ± 9.6 min (range 27–62) for propofol and 41.5 ± 10.3 min (range 31–68) for nitrous oxide. The mean dose requirements were 5.5 ± 1.1 $mg \cdot kg^{-1} \cdot h^{-1}$ (range 3.7–6.6) for propofol and 43.6% ± 4.8% (range 35%–50%) for nitrous oxide. Figure 2 shows mean (±SD) values for arterial blood pressure, heart rate, Sp_{O_2}, and $P_{ET}CO_2$ during propofol and nitrous oxide sedation. Arterial blood pressure did not change significantly in the nitrous oxide group, whereas there was a significant decrease in the patients sedated with propofol. Compared with presedation values, heart rate decreased significantly in both groups (by 9 beats/min). The Sp_{O_2} remained above 95% in the propofol group and remained above 98% in the nitrous oxide group. The $P_{ET}CO_2$ was slightly higher ($P < 0.05$) in the propofol group (40 vs 35 mm Hg in the nitrous oxide group).

The level of consciousness during propofol or nitrous oxide sedation did not exceed sedation score 3 except in one patient, who reached sedation score 4 at the end of the propofol sedation. At that time, a short period of airway obstruction occurred that was immediately detected and corrected. Table 4 shows the blood concentrations of propofol in three patients at the end of sedation.

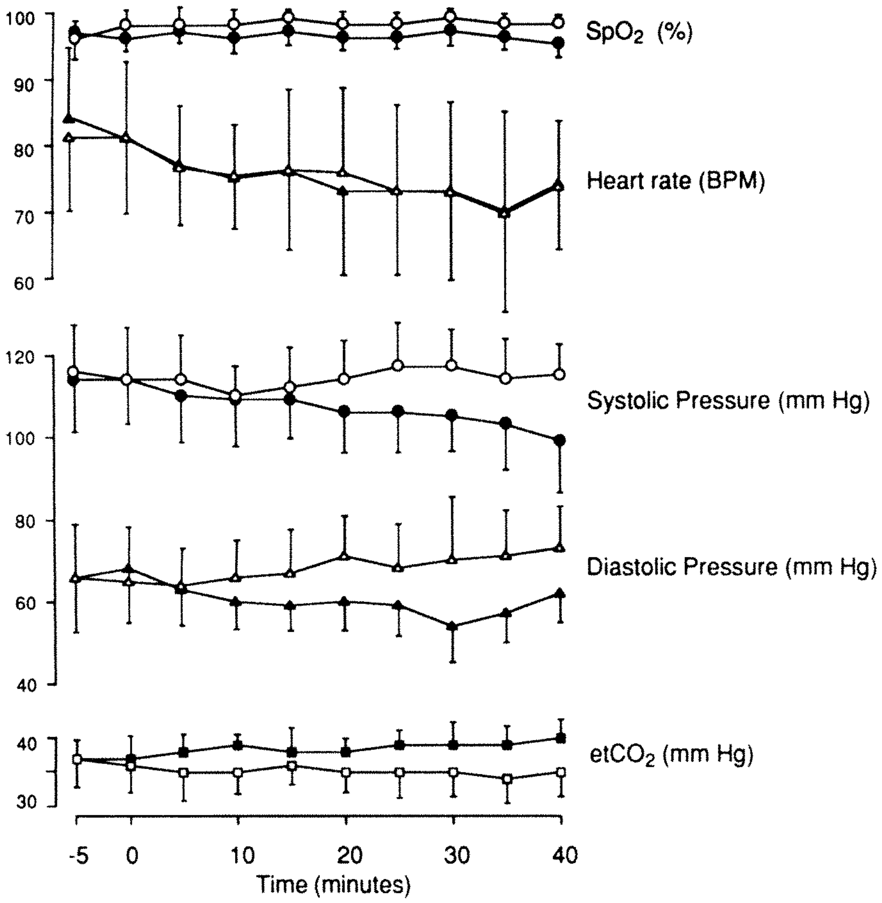

Figure 2. Mean (±SD) hemodynamic and respiratory variables during propofol and nitrous oxide sedation. *Solid symbols*, propofol; *open symbols*, nitrous oxide. Spo_2, oxygen saturation; BPM, beats/min; $etCO_2$ end-tidal CO_2 concentration.

Table 4. Plasma Concentration of Propofol at the End of the Infusion in Three Study Patients

Pt No.	Duration of infusion (min)	Bolus dose (mg/kg)	Infusion rate ($mg \cdot kg^{-1} \cdot h^{-1}$)	Blood conc (μg/mL)
8	62	0.8	3.7	0.6
9	41	0.7	6.2	1.0
11	50	0.8	5.7	1.1

Conc, concentration; Pt, patient.

Discussion

The provision of quality dental care to patients who are severely mentally and physically handicapped is a challenge. Behavior management combined with conscious sedation using nitrous oxide/oxygen has become an established technique for dental treatment in this group of patients. However, a small proportion of these patients cannot be adequately managed by this technique alone, because of restricted coping resources and the inability to carry out continuous nasal breathing, essential for nitrous oxide administration by nasal mask. In a previous study, we demonstrated that propofol by continuous intravenous infusion can be a suitable alternative to nitrous oxide for conscious sedation in dentistry or oral surgery. Sedation with propofol infusion is comparable to nitrous oxide/oxygen inhaled sedation in that recovery is rapid without side effects (6). However, there are conflicting data with respect to the proconvulsive or anticonvulsive properties of propofol. The results of the present study suggest that propofol administered in sedative doses neither provokes seizures nor enhances interictal EEG manifestations in patients with treated epilepsy.

Dystonic reactions have been reported to occur immediately after induction with propofol administered as the sole anesthetic agent in children (7). Opisthotonus and tonic-clonic seizures have been described after emergence from anesthesia with propofol and additional anesthetics (alfentanil and enflurane) (8) and after the use of propofol for sedation in the intensive care unit (9). This involved patients without a history of epilepsy. The EEG, recorded with surface electrodes after the acute states, demonstrated no evidence of epileptic activity. Two studies reported the effects of propofol administration during general anesthesia on the EEG recorded with chronically implanted subdural electrodes in epileptic patients. Hodkinson et al. (10) recorded discharges of epileptiform activity from the previously mapped epileptogenic foci during propofol infusion. They also observed new epileptic activity in other areas of the cortex that had showed no epileptic activity before the injection of propofol. Hufnagel et al. (11) observed maximal suppression of brain activity in the epileptogenic brain area in 12 of 20 patients and also suppression of spontaneous interictal activity present before the onset of anesthesia in 10 of 20 patients; in 5 of 20 patients, there was induction of epileptiform activity. In one patient, a seizure occurred. Our patients were conscious during propofol administration. The EEG recorded from surface electrodes did not show any evidence of increased epileptic activity. There is also considerable evidence that propofol may have anticonvulsive properties. Protection against epileptiform seizures induced by electroshock and pentylenetetrazol in mice was assessed by Lowson et al. (12). They concluded that intraperitoneal administration of propofol (50 mg/kg) has a strong anticonvulsant effect. Several studies comparing propofol and methohexitone in patients receiving electroconvulsive therapy have shown a shorter duration of seizure activity with propofol (13–15). Others have reported the successful use of propofol infusions in the control of intractable status epilepticus, resistant to conventional therapy (16,17). We conclude that the available data are inconclusive with respect to whether propofol administration is associated with enhancement of epileptic activity.

In a review of proconvulsant and anticonvulsant properties of anesthetic drugs, Modica et al. (19,20) concluded that the available evidence with regard to the cerebral stimulatory effects of nitrous oxide suggests that its epileptogenic potential is extremely low. In our study, the EEG was unchanged during nitrous oxide sedation in nine patients, whereas in two patients the frequency of paroxysmal discharges decreased. This suggests that nitrous oxide can be administered safely to patients with treated epilepsy.

In a previous study, we administered propofol for conscious sedation in nonepileptic patients (6). The mean infusion rate of propofol was 3.6 $mg \cdot kg^{-1} \cdot h^{-1}$ (range 2.5–5.4). In the present study, all patients had long-term treatment for epilepsy. Using the same sedation scoring system and titrating propofol to identical endpoints (sedation score 3), the mean infusion rate was 5.5 $mg \cdot kg^{-1} \cdot h^{-1}$ (range 3.7–6.6) in the epileptic patients. It is conceivable that this higher dose requirement is a result of hepatic enzyme induction, as a consequence of long-term antiepileptic medication (21,22).

With both sedative regimens there were no untoward changes in hemodynamic and respiratory variables. In all patients, Spo_2 remained above 95% and was higher during nitrous oxide sedation, as a result of a higher fraction of inspired oxygen. The higher P_{ETCO_2} and slightly lower Spo_2 values during propofol infusion indicate that close supervision of the airway and respiration is necessary. It is especially important not to exceed sedation score 3.

In conclusion, the results of the present study suggest that propofol and nitrous oxide can be administered in subanesthetic doses for conscious sedation in mentally and physically handicapped patients with treated epilepsy undergoing dental procedures. More EEG studies are needed to determine the epileptogenic potential of propofol.

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Venous Air Embolism in Prone Dogs Positioned With the Abdomen Hanging Freely: Percentage of Gas Retrieved and Success Rate of Resuscitation

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Based on reports of fatal venous air embolism (VAE) occurring during lumbar laminectomy and spinal fusion in prone patients positioned with the abdomen hanging freely, it has been recommended that monitoring for VAE should be used for such cases and that a multiorificed central venous catheter should be inserted for aspiration of VAE. The present study was designed to examine aspiration of VAE when prone dogs positioned with the abdomen hanging freely were given a fatal VAE via a femoral vein. Twenty-one dogs were anesthetized with halothane and nitrous oxide in oxygen and positioned with the abdomen ventral and hanging freely, the head fixed in a stereotaxic frame, the upper extremities resting on a surface approximately 10 cm below the level of the stereotaxic frame, and the lower extremities on a surface below the level of the upper extremities (to ensure that VAE entering the inferior vena cava would ascend toward the heart). In the control group (n = 7), a central catheter was placed but was not used to aspirate VAE. In a second group (n = 7), a Cook Bunegin-Albin multiorificed catheter was inserted; and in a third group (n = 7), an American Edwards 7F Swan-Ganz catheter was inserted. Dogs were then given a predetermined lethal dose of air (5 mL/kg) over 30 s via the femoral vein. In groups 2 and 3, attempts to aspirate VAE were begun with the first decrease in expired CO_2. The amounts of gas retrieved (expressed as a percent of the injected air) and the incidence of successful resuscitation were compared. Significantly greater percentages of injected venous air were retrieved with the Bunegin-Albin catheter (47% ± 20% [mean ± SD]) than with the Swan-Ganz catheter (8% ± 6%). However, the success rate of resuscitation was identical whether attempts to aspirate VAE were performed with Bunegin-Albin or Swan-Ganz catheters or no attempt was made to aspirate VAE (1 of 7 survivors in all three groups). It is concluded that in prone dogs positioned with the abdomen hanging freely, central catheters located near the junction of the right atrium and superior vena cava may be ineffective for retrieval of VAE reaching the heart via the inferior vena cava and do not increase the success rate of resuscitation.

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Recently Albin et al. (1) reported two cases of acute, fatal venous air embolism (VAE) in patients in the prone position undergoing lumbar laminectomy and spinal fusion. Both patients had been placed prone on a four-poster frame that allowed the abdomen to hang freely. It was speculated that in this position, the absence of external pressure on the abdominal contents probably resulted in negative pressure in the inferior vena cava (IVC). Negative pressure in the IVC and a considerable gravitational gradient between the vertebra and the right atrium (RA) favored the rapid entrainment of air into the venous circulation. On the basis of these and other reports of VAE in the prone position (2–4), Albin et al. (1) recommended "the need for serious consideration for complete monitoring for VAE whenever a patient is placed prone using any of the positioning techniques that allows for free movement of the abdomen." They stated that monitoring should include a multiorificed central venous catheter for aspiration of VAE, with the catheter tip localized at either the RA-superior vena cava (SVC) junction or at 2 cm in the RA.

Previous studies from my laboratory reported on the use of central catheters for aspiration of VAE in other positions. In three studies (5–7), dogs were placed in the upright position, a multiorificed central venous catheter or a pulmonary artery (PA) catheter, or both, were positioned near the location recommended by Albin et al. (1), and a lethal dose of air was injected into the jugular vein. In a fourth study

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(8), dogs were placed prone lying on their chest and abdomen, a multiorificed central venous catheter or a PA catheter was positioned near the location recommended by Albin et al. (1), and a lethal dose of air was injected into the femoral vein. In all four studies, the catheters were aspirated after VAE, and the volume of gas retrieved and the success rate of resuscitation were determined.

There have been no reports on the volume of gas aspirated and the success rate of resuscitation after lethal VAE in prone dogs positioned so that the abdomen hangs freely. The present study was designed to examine the efficacy of the two most commonly studied catheters, a Cook Bunegin-Albin multiorificed central venous pressure (CVP) catheter and a 7F American Edwards Swan-Ganz catheter, for gas aspiration and resuscitation in prone dogs with a freely hanging abdomen.

Methods

The experimental protocol was similar to that outlined in four previous studies from this laboratory (5–8). The study was approved by the Institutional Animal Care Committee, and 21 dogs (weight 15–22 kg) were anesthetized with 2% inspired halothane and 66% N_2O in O_2. The dogs' lungs were ventilated to maintain Pa_{O_2} >120 mm Hg and Pa_{CO_2} at 35–40 mm Hg. Expired CO_2 was continuously monitored using a Capnogard model 1250 End Tidal Monitor (Novametrix Medical Systems Inc.). An electronic offset was used to minimize interference by expired N_2O on the strip-chart recorder display. The right jugular vein was cannulated with either a Cook Bunegin-Albin multiorificed catheter or a 7F American Edwards Swan-Ganz catheter for measurement of RA pressure or CVP and, where appropriate, retrieval of injected air. The right femoral vein was cannulated for fluid administration and injection of air. A femoral artery was cannulated for sampling of blood to measure hemoglobin and gas tensions and for continuous monitoring of systemic arterial pressure and heart rate. Mean arterial pressure was determined by electronic integration. Temperature was monitored by a nasopharyngeal thermistor probe and maintained at 37.0 ± 0.5°C by heat lamps or ice packs. Vascular volume was maintained by continuous infusion of saline (4–6 $mL \cdot kg^{-1} \cdot min^{-1}$).

At the conclusion of the surgical preparation, wound edges were infiltrated with 0.5% bupivacaine, and the concentration of halothane was decreased to 0.5% inspired (%N_2O unchanged). Dogs were positioned with the abdomen ventral and hanging freely, the head fixed in a stereotaxic frame, the upper extremities resting on a surface approximately 10 cm below the level of the stereotaxic frame, and the lower extremities on a surface below the level of the upper extremities. Thus, in this study the trunk was positively inclined in the cephalad direction, unlike previous studies from this laboratory, where the head was elevated but the trunk was positioned horizontally (8). This position was chosen so that the IVC would be positively inclined toward the RA, assuring that VAE entering the IVC would ascend toward the RA (due to the buoyancy of air) and not simply collect in the engorged abdominal vessels. Up to 200 mL of saline was administered to achieve a mean RA pressure or CVP of approximately 2 mm Hg with the transducer zeroed at the RA. Once systemic variables had stabilized (25 min after decreasing halothane to 0.5%), baseline values for systemic variables were recorded. These included CVP or RA pressure, PA occlusion pressure, mean arterial pressure, heart rate, arterial blood gas tensions, arterial blood hemoglobin levels, and nasopharyngeal temperature.

Dogs were randomly assigned to one of three groups. In the control group ($n = 7$), a Bunegin-Albin multiorificed catheter ($n = 4$) or a Swan-Ganz catheter ($n = 3$) was inserted and was used to measure CVP but was not used for aspirating air. In the second group ($n = 7$), a Bunegin-Albin multiorificed catheter was inserted for measurement of CVP and was used for aspirating air. In the third group ($n = 7$), a Swan-Ganz catheter was inserted for measurement of PA occlusion pressure and RA pressure and was used for aspirating air. As in previous studies from this laboratory, the Bunegin-Albin and Swan-Ganz catheters were examined in the position reported by Bunegin et al. (9) as optimum for aspirating air when VAE entered through the SVC. With the Bunegin-Albin catheter, the proximal orifice was placed near the SVC-RA junction and distal orifice near the mid-RA. With the Swan-Ganz catheter, the RA port was positioned near the SVC-RA junction, and the PA port was placed in the PA. Catheters were positioned by using the catheter as an exploring electrocardiographic lead (10) and, for the Swan-Ganz catheter, using the PA pressure trace to confirm placement of the PA port in the PA.

The multiorificed portion of the Bunegin-Albin catheter and the RA port of the Swan-Ganz catheter were advanced until the point of maximal negative P-wave deflection with no positive P-wave component. This point was taken to indicate that the multiorificed portion of the Bunegin-Albin catheter and the RA port of the Swan-Ganz catheter were at the SVC-RA junction. The Bunegin-Albin catheter was advanced 1–2 cm once the point of maximal P-wave deflection was reached. Because the proximal and distal orifices are approximately 5 cm apart, this maneuver placed the proximal orifice approximately 1 cm above the SVC-RA junction and the distal orifice

Table 1. Systemic Variables in the Three Study Groups

	Controls ($n = 7$)	Bunegin-Albin multiorifice catheter ($n = 7$)	Swan-Ganz catheter ($n = 7$)
Pa_{O_2} (mm Hg)	139 ± 22	141 ± 16	138 ± 14
Pa_{CO_2} (mm Hg)	37.9 ± 1.8	37.9 ± 1.9	37.4 ± 1.8
pH	7.36 ± 0.04	7.37 ± 0.02	7.36 ± 0.03
Bicarbonate (mEq/L)	20.7 ± 0.8	21.5 ± 1.3	21.3 ± 1.5
Hemoglobin (g/dL)	12.8 ± 1.5	13.2 ± 2.1	13.3 ± 2.0
Mean arterial blood pressure (mm Hg)	106 ± 20	103 ± 20	105 ± 18
Central venous pressure (mm Hg)	3 ± 1	2 ± 1	3 ± 2
Pulmonary artery occlusion pressure (mm Hg)	—	—	8 ± 5
Heart rate (beats/min)	105 ± 14	100 ± 18	107 ± 13
Temperature, nasopharyngeal (°C)	37.2 ± 0.5	37.1 ± 0.5	37.2 ± 0.5

Values are mean ± SD.

in the mid-RA (10). The RA port of the Swan-Ganz catheter was withdrawn approximately 1–2 cm once the point of maximal P-wave deflection was reached.

The dose of air chosen for injection in this study was 5 mL/kg. This dose was chosen on the basis of previous reports from this laboratory that 5 mL/kg was the mean fatal VAE for dogs in both the prone and upright positions when doses of 3, 5, or 7 mL/kg of air were administered intravenously (5,6,8). In this study, as in the previous ones, 5 mL/kg of air was injected over 30 s. Resuscitation was not attempted in the control group but was attempted in the other two groups. The only method of resuscitation used was aspiration of VAE. Attempts to retrieve VAE were made using 50-mL syringes attached to the catheter. One syringe was used with the Bunegin-Albin catheter, and two syringes (one for the RA port and one for the PA port) were used with the Swan-Ganz catheter. Aspiration was begun as soon as expired CO_2 decreased after injection of air. With the Swan-Ganz catheter, both syringes were aspirated simultaneously. The "plunger" of the 50-mL syringe was pulled back manually with as much force as could be generated by hand. The negative force generated during aspiration was not measured. Aspiration was continued until gas no longer was seen to be entering the syringe. In cases where large amounts of gas were retrieved, an additional 50-mL syringe was used. Invariably, blood was aspirated, but because the amount of blood was small (10–40 mL) and in previous studies was not significantly different among groups (5–8), no attempt was made to reinfuse the aspirated blood.

The volume of gas retrieved was expressed as a percent of injected air. The term "gas" is used because the retrieved gas was comprised of both the injected air and whatever amount of N_2O might have diffused into the injected air. In the present study, this percent and systemic variables were compared among groups by use of analysis of variance. The incidence of successful resuscitation among groups and the percentage of VAE that was retrieved in survivors and nonsurvivors was compared using the variance ratio test (11). A P value <0.05 was considered statistically significant. Values are reported as mean ± SD.

Table 2. Retrieval of Intravenously Injected Air and Success Rate of Resuscitation in the Three Study Groups

	Controls ($n = 7$)	Bunegin-Albin multiorifice catheter ($n = 7$)	Swan-Ganz catheter ($n = 7$)
Air injected (mL)	100 ± 8	89 ± 8	95 ± 8
Air retrieved (%)	0	47 ± 20^a	8 ± 6
Air plus blood retrieved (mL)	0	89 ± 15^a	22 ± 8
Proportion of surviving dogs	1/7	1/7	1/7

Values are mean ± SD or number.
^{a}Significantly different from Swan-Ganz catheter; $P < 0.05$.

Results

There were no differences among groups with respect to systemic circulatory variables or blood chemistries before infusion of air (Table 1).

A significantly greater amount of gas as a percent of the 5-mL/kg VAE dose was retrieved using the Bunegin-Albin catheter (47% ± 20%) than either with the Swan-Ganz RA and PA ports (8% ± 6%) or in the control dogs, where no attempt was made to retrieve VAE (0%) (Table 2). Also, a significantly greater volume of air plus blood was retrieved using the Bunegin-Albin catheter (89 ± 15 mL) than either with the Swan-Ganz RA and PA ports (22 ± 8 mL) or in the control dogs, where no attempt was made to aspirate air or blood (0 mL). The incidence of successful resuscitation from VAE did not differ among groups (one of seven dogs in all three groups).

Discussion

The present results are consistent with previously reported findings from this laboratory in prone dogs given VAE via the femoral vein and in upright dogs given VAE via the jugular vein (6–8). The results of those studies and the present one indicate that the choice of venous catheter may have clinical implications for aspiration of venous air. In this study, as in the previous ones, the Bunegin-Albin multiorificed catheter and not the Swan-Ganz catheter allowed retrieval of a large percentage of intravenously infused air. Similar findings for the Swan-Ganz catheter were reported by Sink et al. (12) in both prone and upright dogs given VAE via the jugular vein.

In contrast to previously reported findings from this laboratory, the incidence of successful resuscitation in this study was not directly related to the amount of air retrieved (5–8). Also in contrast to previous studies, in the present study the Bunegin-Albin catheter did not increase the rate of successful resuscitation from a lethal dose of venous air. The differences in results between this and previous studies probably relate to site of air entry, body position, and catheter location.

In upright dogs given VAE via the jugular vein, use of the Bunegin-Albin multiorificed catheter or a modified Arrow prototype multiorificed catheter permitted 63% ± 14% (mean ± SEM) or 73% ± 13% (mean ± SD), respectively, of injected venous air to be retrieved and four of six dogs (with either catheter) to be successfully resuscitated (6,7). Presumably, in the upright position the buoyancy of gas acts along the axis of the SVC so that VAE disperse into zones of high flow velocity. In the case of VAE entering the heart via the SVC, it has been demonstrated by echocardiography that SVC flow carries VAE to the SVC-RA junction, where the air tends to localize (13). After accumulating at the SVC-RA junction, small VAEs break off from large bubbles to move through the tricuspid valve or into the upright portions of the RA. A relatively long time is available for aspiration via a SVC-RA catheter.

In prone dogs lying on their chest and abdomen, with the head elevated and the trunk positioned horizontally, that were given VAE via the femoral vein, use of the Bunegin-Albin multiorificed catheter permitted 60% ± 7% (mean ± SEM) of injected venous air to be retrieved and six of nine dogs to be successfully resuscitated (8). Presumably, in the prone position, the buoyancy of gas favors accumulation of VAE against the nondependent (superior) walls of the IVC and RA. Because these are zones of low flow velocity, VAE may not be quickly "washed away," and a relatively long time may be available for aspiration via a SVC-RA catheter.

In the present study, dogs were positioned prone with the abdomen hanging freely and the head and upper extremities higher than the lower extremities. Venous air embolism was injected via the femoral vein, and the Bunegin-Albin multiorificed catheter permitted 47% ± 20% of injected air to be retrieved and one of seven dogs to be successfully resuscitated. The numerically smaller percentage of injected air retrieved in this study compared with the previous ones (6–8) suggests that air injected into the femoral vein of prone dogs with the abdomen hanging freely either (a) in part remains in engorged abdominal vessels or (b) does not localize at a site from which it can be easily aspirated via a catheter positioned in the mid to high RA. The first proposal, that abdominal vessels engorged because of the negative pressure in the IVC with absence of external pressure on the abdomen (1) "trap" a portion of the air injected into the femoral vein, seems unlikely considering the present findings. If a portion of the air injected into the femoral vein remained in engorged abdominal veins, the percent of injected air that was retrieved would be low (as was observed), but also the percentage of animals killed by 5 mL/kg of injected air would be significantly <100%, contrary to the present finding that only one of seven control dogs survived. The high death rate in controls after 5 mL/kg of air was injected into the femoral vein suggests that VAE dispersed into the IVC and ascended into the heart. There are no reported echocardiographic studies in the upright position of VAE entering the heart via the IVC. However, it seems likely that IVC flow carries VAE to the IVC-RA junction where air either localizes (assuming flow patterns at this junction similar to those at the SVC-RA junction), moves through the tricuspid valve (following the principal path of IVC flow), or ascends (against the principal path of RA flow) to the upright portion of the RA. Presumably, IVC and thoracic pressure at end expiration is more positive in prone dogs lying on their chest and abdomen than in prone dogs with their chest and abdomen hanging freely, and this pressure opposes localization of VAE at the IVC-RA junction or movement through the tricuspid valve, or both, and favors ascent into the superior RA, accounting for the numerically smaller percentage of VAE retrieval in this study.

That retrieval of large amounts of VAE increases the likelihood of surviving a fatal dose of air can be appreciated from this study and the previous ones from this laboratory. In the four previous studies, >62% of injected air was retrieved with a multiorificed device in 21 of 39 dogs, and 23 of 39 dogs survived (5–8). The percentage of injected air retrieved and the success rate of resuscitation were significantly increased compared with control dogs, where none of the injected air was retrieved and 1 of 25 dogs survived. In the present study, >62% of injected air was retrieved in one of seven dogs, and that dog survived. The survival rate was not different from control dogs (one of seven).

It should be noted that in this model, VAE was administered as a bolus dose. In the clinical situation, VAE is considered to occur most commonly as a continuous entrainment of small quantities of air. This difference may limit extrapolation from the present study to the clinical setting. To the extent that the results of this study are relevant to the clinical setting, they may have implications for the clinical care of prone patients positioned with their abdomen hanging freely compared with prone patients lying on their chest and abdomen and with patients in the sitting position.

The present results suggest that, with a catheter placed in the mid or high RA and the trunk positively inclined in the cephalad direction, IVC VAE may be more difficult to aspirate in prone patients positioned with their abdomen hanging freely than in patients in the other positions. The present results also suggest that with a catheter in the mid or high RA and the trunk positively inclined, retrieval of IVC VAE in prone patients with their abdomen hanging freely may not provide a greater likelihood of successful resuscitation than when no attempt is made to retrieve IVC VAE. Additional studies are needed to determine whether the finding of difficult resuscitation from lethal VAE in prone dogs positioned with their abdomen hanging freely is reproducible in other species, with other volumes and rates of infusion of VAE, with the air aspiration catheter in other locations, and with other body positions. If so, the difficulty of resuscitation from VAE in this position should be mentioned when informed consent is obtained from patients scheduled for surgery in this position, and efforts should be made to modify patient position or other surgical conditions to minimize the likelihood of VAE occurring. Additional studies also are needed to determine whether positioning of a multiorifice central venous catheter in a location other than near the SVC-RA junction would improve the percentage of IVC VAE retrieval and also improve the success rate of resuscitation from VAE.

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Effect of Halothane, Fentanyl, and Ketamine on the Threshold for Transpulmonary Passage of Venous Air Emboli in Dogs

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We assumed that the capacity of the lungs to filter gas bubbles would vary as a function of anesthetic management. The effects of halothane (1% inspired concentration [group 1, $n = 8$]), fentanyl (100 μg/kg IV, followed by 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ [group 2, $n = 7$]), and ketamine (10 mg/kg IV, followed by 0.2 $mg \cdot kg^{-1} \cdot min^{-1}$ [group 3, $n = 6$]) on the passage of bolus injections of air across the pulmonary circulation were studied in dogs by using transesophageal echocardiography to detect air in the left atrium or the aorta, or both. The thresholds for bolus air detection during halothane, fentanyl, and ketamine administration were 0.05 mL/kg (range 0.01–0.1), 0.5 mL/kg (range 0.2–1.0), and 0.35 mL/kg (range 0.1–0.5), respectively. We conclude that the threshold during fentanyl- or ketamine-induced anesthesia was significantly higher than during halothane-induced anesthesia. Therefore, halothane interferes with the capacity of the lungs to filter air from the pulmonary circulation.

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The lungs are an important physiologic filter for venous air emboli. This filtering capacity can be impaired by overloading the pulmonary vessels with gas infusion (1–3) and by the use of drugs (2) or anesthetics (4–6). In a previous study, we demonstrated that the threshold for transpulmonary passage of a venous air embolism was higher during pentobarbital-induced anesthesia, with or without halothane, than during anesthesia with halothane alone (4). We did not determine whether halothane decreased or pentobarbital increased the threshold compared with unanesthetized animals, because the transesophageal echocardiographic probe could not be successfully used in awake dogs. However, the study demonstrated that anesthetics could exert important effects on the outcome of both clinical and experimental venous air emboli.

Fentanyl and ketamine have been extensively used as intravenous anesthetics both in humans and in laboratory animals; however, there have been no previous reports concerning the influence of these anesthetics on outcome after venous air embolism. In this study, we assessed the effects of fentanyl and ketamine on the threshold for transpulmonary passage of venous air emboli in dogs.

Methods

Twenty-one mongrel dogs weighing between 10 and 15 kg (12.0 ± 1.0 kg [mean ± SD]) were studied in a protocol approved by the Institutional Animal Care and Use Committee. Animal care followed the institutional guidelines for animal experimentation.

The dogs were randomly separated into three groups that were anesthetized with halothane (group 1, $n = 8$), fentanyl (group 2, $n = 7$), and ketamine (group 3, $n = 6$). Anesthesia was induced with halothane (2%–4% inspired concentration) administered by mask, intravenous fentanyl (100 μg/kg) over 20 min, or intravenous ketamine (10 mg/kg) over 20 min. The dogs were placed in the supine position. After tracheal intubation, their lungs were mechanically ventilated with a mixture of oxygen/nitrogen (1:2) to achieve a Pa_{CO_2} of 35–40 mm Hg. After induction, anesthesia was maintained using the following doses: halothane, 1.0% inspired concentration; fentanyl, 1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$; or ketamine, 0.2 $mg \cdot kg^{-1} \cdot min^{-1}$. The dogs were paralyzed with pancuronium bromide (0.2 mg/kg), with supplemental doses administered every hour. The esophageal temperature was maintained at 37.5 ± 0.5°C with a heating blanket and an infrared light.

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Under topical anesthesia with 1% lidocaine, the following procedures were undertaken. A 5F pulmonary artery thermodilution catheter (Edwards Laboratories, Inc., Santa Ana, Calif.) was inserted into the main pulmonary artery through the femoral or the right external jugular vein. A 5F pigtail catheter (Cook Group Company, Bloomington, Ind.) was inserted into the left ventricle through the right carotid artery to measure the left ventricular end-diastolic pressure. Another catheter was inserted through the left external jugular vein into the right atrium to measure the right atrial pressure. For systemic arterial pressure measurements and blood sampling, a catheter was inserted in a femoral artery. A 3.5-MHz transesophageal M-mode/two-dimensional, changeable echocardiographic probe (Aloka Industries Ltd., Tokyo, Japan), interfaced with an echoinstrument (model SSD-110, Fukuda Denshi Inc., Tokyo, Japan), was inserted into the esophagus for air detection (4,7,8). The probe was positioned so that the left atrium and the aortic cavity could be visualized simultaneously with the M mode. The diameter of the air bubbles at the tip of the pulmonary artery catheter varied between 1.4 and 3.0 mm when infused into stationary saline at an air dose of 1.4 and 180 mL/min, as verified by a microvideoscopic technique (Zeiss, Zurich, Switzerland and Hitachi, Tokyo, Japan).

After a 30-min period of stabilization under the selected anesthetic conditions, control hemodynamic measurements were made, and 0.2 mL/kg of air was injected over a 5-s period through the pulmonary artery port of the pulmonary artery catheter to avoid passage through possible intracardiac septal defects. The presence of air in the left atrium or the aorta, or both, was validated by a scratchlike or flufflike appearance on the echocardiogram by an observer who was unaware of the type of study anesthesia. If no air was detected, additional bolus doses of 0.5 and 1.0 mL/kg were injected. At least 20 min was allowed between incremental air injections. If air was detected on the echocardiogram after a 0.2-mL/kg injection of air, decreasing doses of 0.1, 0.05, and 0.01 mL/kg of air were injected. In each dog, the minimal quantity of injected air required for detection in the left atrium or the aorta, or both, was regarded as the threshold value for transpulmonary passage of venous air.

Mean arterial pressure, right atrial pressure, mean pulmonary arterial pressure (MPAP), heart rate, cardiac output (CO), and left ventricular end-diastolic pressure (LVEDP) were measured before (as the baseline value for each air injection) and 30 s after air injection. Body surface area (BSA) (m^2) was calculated as $0.112 \times \text{weight (kg)}^{2/3}$. Cardiac index (CI) was defined as CO/BSA. Pulmonary vascular resistance index (PVRI, $\text{dyne}\cdot\text{s}\cdot\text{cm}^{-5}\cdot\text{m}^2$) was calculated as (MPAP − LVEDP) × 79.9/CI. To calculate ve admixture, arterial and mixed venous blood sa were obtained simultaneously in plastic prehe ized syringes and iced immediately before analyzed within 10 min on an automated ana (ABL2, Radiometer, Copenhagen, Denmark). rial blood gas tensions were corrected for body perature. Alveolar oxygen tension (P_{AO_2}) was lated using the formula:

$$P_{AO_2} = (P_B - P_{H_2O})(F_{IO_2}) - P_{aCO_2}/R,$$

where F_{IO_2} is the fraction of inspired oxygen, the arterial carbon dioxide partial pressure, P barometric pressure, and R the respiratory quo assumed to be 1.0. Water vapor pressure (P_{H_2O} corrected for temperature. A standard shunt fo was used for calculating the shunt fraction:

$$Qs/Qt = 100 \times (Cc_{O_2} - Ca_{O_2})/(Cc_{O_2} - C\bar{v}_{O_2}),$$

where Qs/Qt is the shunt fraction, Cc_{O_2} the calc capillary oxygen content obtained from the al air equation, Ca_{O_2} the arterial oxygen content lated as (1.35 × hemoglobin × % saturation) + × P_{AO_2}, and $C\bar{v}_{O_2}$ the mixed venous oxygen co calculated using $P\bar{v}_{O_2}$ obtained from the pulm artery catheter.

The threshold data were analyzed using the Kr Wallis test for analysis of variance and the Whitney U-test. The baseline hemodynamic before each bolus air injection within each anes procedure were compared using an analysis of va for all measurements. When there was no diff among the baseline values, the individual val bolus air injection was compared with its baseline (the value before the air injection) by the paire dent's *t*-test. Comparisons of the hemodynamic obtained during halothane anesthesia (a control during the other anesthetic procedures were perf using Dunnett's method. $P < 0.05$ was consi significant for all tests.

Results

The bolus doses of air required for passage in systemic circulation are shown in Table 1. Duri halothane anesthesia, the threshold was 0.05 m The threshold with fentanyl (0.5 mg/kg) or ket (0.35 mg/kg) was significantly greater. There w significant difference between the threshold d anesthesia with fentanyl or ketamine. No an died during air injection.

The MPAP and PVRI increased significantl ing each bolus air injection at each dose (>0.1 m with each agent. In dogs anesthetized with fe and ketamine, MPAP and PVRI increased more in halothane-anesthetized dogs. The shunt fr

Table 1. Threshold Values of Transpulmonary Passage of Venous Air Emboli in the Three Study Groups

Dog No.	Halothane (mL/kg)	Dog No.	Fentanyl (mL/kg)	Dog No.	Ketamine (mL/kg)
H1	0.01	F1	0.2	K1	0.5
H2	0.05	F2	1.0	K2	0.2
H3	0.01	F3	0.2	K3	0.1
H4	0.05	F4	0.5	K4	0.2
H5	0.05	F5	1.0	K5	0.5
H6	0.05	F6	0.2	K6	0.5
H7	0.05	F7	1.0		
H8	0.05				
Median	0.05		0.5^a		0.35^a

[a] $P < 0.05$ compared with halothane.

increased significantly from baseline in dogs anesthetized with halothane or ketamine (Table 2).

Mean arterial pressure and heart rate did not change significantly after air injection in any group.

Discussion

This study demonstrated that during halothane-induced anesthesia, the threshold for transpulmonary passage of bolus injections of air into the pulmonary artery was lower (0.05 mL/kg) than that observed during anesthesia with fentanyl (0.5 mL/kg) or ketamine (0.35 mL/kg) (Table 1). These results suggest that the lung is an effective filter for gas bubbles during administration of these intravenous anesthetics and that this filtering ability is greatly impaired by the use of halothane. We have previously shown that pentobarbital also increased the threshold for air passage compared with that during halothane anesthesia (4). These two studies showed the lower filtering ability of air during halothane anesthesia.

The mechanism by which anesthetics influence the threshold for transpulmonary passage of venous air embolism is unknown but may be mediated through effects on pulmonary blood flow at the level of the arterioles, shunt vessels, or capillaries. Every bolus injection >0.1 mL/kg increased the MPAP and PVRI during all anesthetics, and fentanyl- and ketamine-anesthetized dogs showed a greater increase in MPAP and PVRI compared with halothane-anesthetized dogs (Table 2). Because the arteriole is the major determinant of MPAP and PVRI, we might expect an arteriolar effect to be reflected in this change in MPAP and PVRI. In previous studies in pentobarbital-anesthetized dogs, air bubbles lodged in pulmonary arterioles were eliminated from that site (9) in proportion to the MPAP level (10,11).

Furthermore, the threshold for transpulmonary passage of air in the halothane-anesthetized dogs was smaller (0.12–0.75 mL) and showed no apparent change in any pulmonary measurement or calculation. Based on the conditions of our study, we cannot speculate about contributing mechanisms, such as inhibition of hypoxic pulmonary vasoconstriction (5) or opening of possible intrapulmonary shunts such as the Sperr arteries (12) during halothane anesthesia.

Anesthetic effects on transpulmonary arteriovenous shunting were analyzed by Cheney et al. (13) who measured shunt fraction during venous embolism in pentobarbital-anesthetized dogs using a radioactive microsphere technique. During embolism, pentobarbital caused a 2.5-fold increase of PVRI relative to control dogs, with no effect on cardiac output or shunt fraction. This results in an increase of resistance against emboli to passage through the shunt fraction, which may coincide with the increased threshold of the transpulmonary passage of bolus injections of air into the pulmonary artery in pentobarbital-anesthetized dogs (4).

We did not use additional bolus injections of air much larger than the threshold dose so as to avoid the possible deterioration of the pulmonary vasculature

Table 2. Mean Pulmonary Artery Pressure, Pulmonary Vascular Resistance Index, and Intrapulmonary Shunt Response for Every Bolus Air Injection in the Three Study Groups

Dose of air (mL/kg)	MPAP (mm Hg)			PVRI (×10^2 dyne·s·cm^{-5}·m^2)			Qs/Qt (×100%)		
	Halothane	Fentanyl	Ketamine	Halothane	Fentanyl	Ketamine	Halothane	Fentanyl	Ketamine
Baseline	15.8 ± 2.8	17.1 ± 0.8	20.7 ± 3.4^b	2.4 ± 0.5	2.2 ± 0.9	2.5 ± 0.2	10 ± 1	11 ± 4	10 ± 1
0.2	19.6 ± 4.4^a	22.9 ± 5.0^{a,b}	25.3 ± 4.1^{a,b}	3.0 ± 0.9^a	3.1 ± 1.1^a	4.0 ± 0.7^{a,b}	15 ± 4^a	11 ± 3^b	16 ± 5^a
Baseline	15.6 ± 2.3	16.4 ± 2.2	20.3 ± 3.8^b	2.4 ± 0.6	2.3 ± 0.8	2.7 ± 0.6	10 ± 1	10 ± 1	11 ± 2
0.1	17.9 ± 3.7^a			2.8 ± 0.7^a			13 ± 3^a		
Baseline	16.2 ± 2.3			2.4 ± 0.6			9 ± 1		
0.5		23.8 ± 2.8^a			3.7 ± 1.5^a			14 ± 6^a	
Baseline		16.6 ± 0.8			2.3 ± 0.8			10 ± 2	

MPAP, mean pulmonary artery pressure; PVRI, pulmonary vascular resistance index; Qs/Qt, intrapulmonary shunt fraction.
Values are mean ± SD. There were no differences between baseline values within each anesthetic procedure (analysis of variance).

[a] $P < 0.05$ compared with baseline just before each bolus air injection by paired *t*-test.

[b] $P < 0.05$ compared with halothane.

by repetitive air embolism. Furthermore, quantitative assessment of air in the left heart was difficult using transesophageal echocardiography. Therefore, we could not compare the effects of embolism of much larger doses of air among anesthetics; however, our data permit speculation that fentanyl or ketamine may protect against paradoxical air embolism relative to halothane anesthesia. Further studies are indicated to assess the effects of other intravenous and inhaled anesthetics.

This potential prophylactic effect may merit consideration among the many factors involved in selection of an anesthetic regimen, particularly in surgical procedures thought to have the highest risk for venous air embolization, such as craniectomy, cardiac surgery or right ventriculotomy, and peritoneal insufflation, especially considering the increasing popularity of laparoscopic techniques in general surgery that use hyperbaric gas insufflation (14,15).

In summary, we found that during fentanyl or ketamine anesthesia, the threshold doses for the transpulmonary passage of bolus injections of air into the pulmonary arteries of dogs were significantly higher than during anesthesia with halothane.

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Isoflurane and Nitrous Oxide: Comparative Impact on Cerebrospinal Fluid Pressure in Patients With Brain Tumors

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The relative effects on cerebrospinal fluid pressure (CSFP) of equipotent concentrations of isoflurane and N_2O were compared in 20 patients with brain tumors who had lumbar subarachnoid catheters in place. Patients were randomly assigned to receive one of two anesthetic sequences: group 1, 0.7% end-tidal isoflurane in O_2, which was changed to 70% N_2O in O_2; or group 2, 70% N_2O in O_2, which was changed to 0.7% end-tidal isoflurane in O_2. End-tidal Pco_2 and percent end-tidal N_2O and isoflurane were monitored by mass spectrometry from just before changing anesthetics (time = 0 min) until the end of a 20-min observation period (time = 20 min). Ventilation was held constant at $Paco_2 = 36 \pm 1$ mm Hg (mean ± SE). The patients in group 1 sustained an increase in CSFP that reached a maximum of 33% above the value at 0 min, despite a 3-mm Hg decrease in $Paco_2$ ($P < 0.05$). By contrast, CSFP remained unchanged in group 2. Although the absolute increase in CSFP after replacement of isoflurane/O_2 by N_2O/O_2 anesthesia was relatively small (9 ± 1 to 12 ± 2 mm Hg; $P < 0.05$), the absence of a similar effect in patients where N_2O was replaced by isoflurane suggests that replacement of isoflurane by an equipotent concentration of N_2O is more likely to lead to an increase in CSFP in patients with altered intracranial dynamics than is replacement of N_2O by isoflurane.

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Virtually all inhaled anesthetics are capable of causing undesirable increases in cerebrospinal fluid pressure (CSFP) in patients who have compromised intracranial elastance. Despite this, these drugs are often chosen for patients undergoing craniotomy. At the present time, both N_2O and isoflurane are widely used in neuroanesthesia practice, although both agents are associated with increases in CSFP, even if combined with hyperventilation (1,2). Recent studies of cerebral blood flow (CBF) in humans (3) and rodents (4) indicate that N_2O is a more potent cerebral vasodilator than is an equipotent dose of isoflurane. Because changes in CBF do not always correlate with changes in CSFP, and even small differences in cerebrospinal fluid dynamics may be important in patients who have critical intracranial lesions, we compared the impact of equipotent doses of isoflurane and N_2O on CSFP in patients with brain tumors, using a randomized, crossover protocol, with each patient serving as his or her own control.

Methods

The subjects of this study were 20 patients scheduled for excision of supratentorial tumors not located near the base of the skull. The protocol was approved by the local Institutional Review Board, and written, informed consent was obtained from each patient on the evening before surgery. The preoperative computed tomography scan of each patient's head was evaluated with regard to the following features: (a) widest diameter of tumor (mm); (b) lateral shift of midline structures (mm); and (c) amount of peritumoral edema on a scale of 0–3+, where 1+ = a small rim of edema, 2+ = a wide rim of edema, and 3+ = edema extending throughout the ipsilateral hemisphere.

All patients received dexamethasone (20 mg/day) for a period of 3–4 wk before surgery. Preoperatively, all were alert, verbally responsive, and oriented; none had neurologic signs of elevated CSFP before induction of general anesthesia.

No premedication was administered. General anesthesia was induced with thiopental (5 mg/kg IV) in divided doses; vecuronium (0.1 mg/kg) was used to facilitate endotracheal intubation; and ventilation was controlled to maintain a constant end-tidal CO_2 ten-

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Table 1. Demographic Data for the Two Patient Groups

Anesthetic sequence	Pt age (yr)	Primary tumors	Secondary tumors	Tumor diameter (mm)	Brain edema scale (0–3+)[a]	Midline shift (mm)
Group 1 (isoflurane to N_2O; *n* = 10)	51 ± 5	5	5	31 ± 3	1 ± 0.3	5 ± 1
Group 2 (N_2O to isoflurane; *n* = 10)	51 ± 5	6	4	35 ± 6	2 ± 0.3	5 ± 2

Values are mean ± SE or number.

[a] 1+ = small rim of edema; 2+ = wide rim of edema; 3+ = edema extending throughout the ipsilateral hemisphere.

sion between 30 and 35 mm Hg (Perkin-Elmer Mass Spectrometer).

Patients were randomly assigned to one of two anesthetic techniques: group 1, 0.7% end-tidal isoflurane in O_2; and group 2, 70% N_2O in O_2. After anesthesia was induced, a 20-gauge radial artery catheter and an 18-gauge lumbar subarachnoid catheter were inserted for continuous monitoring of blood pressure and CSFP, respectively. Pressure transducers were zeroed to the level of the midcranium. Continuity of the cerebrospinal fluid compartment was verified by an elevation in CSFP with elevation of the patient's head. Heart rate was determined from electrocardiographic lead II.

During a period of stable hemodynamics and absent surgical stimulation (approximately 30 min after induction of anesthesia), baseline heart rate, blood pressure, and CSFP were recorded, and a blood sample for determination of arterial blood gas tensions was collected anaerobically. Immediately thereafter, at time (T) = 0 min, the inspired anesthetic was abruptly changed as follows: in group 1, isoflurane was discontinued, and 70% N_2O in O_2 was begun; in group 2, N_2O was discontinued, and isoflurane, 1%–2% inspired concentration, was adjusted such that end-tidal isoflurane concentration was constant at 0.7%. The fresh-gas flow rate was 10 L/min throughout the study to facilitate rapid uptake and elimination of anesthetics.

After the change in anesthetic, CSFP and cardiovascular variables were recorded continuously during a 20-min observation period. End-tidal N_2O and isoflurane concentrations were tabulated, and arterial blood gas tensions were determined just before changing anesthetics (T = 0 min) and at the end of the 20-min observation period (T = 20 min). Throughout the data collection period, end-tidal CO_2 tension was held constant, and external sensory stimuli were avoided. After acquisition of data was completed, each patient was hyperventilated to lower CSFP to approximately 5 mm Hg (end-tidal P_{CO_2} = 20–25 mm Hg). Anesthesia was supplemented with either an opioid or additional isoflurane, and surgery commenced.

Data acquired at T = 0 and 20 min were subjected to statistical comparisons using analysis of variance for repeated measures and Student's *t*-test for paired and nonpaired data, as appropriate. Furthermore, to minimize the effect of minute-to-minute variability, CSFP measurements obtained after T = 0 min were averaged over four successive 5-min periods. These four averages were then subjected to repeated measures analysis of variance to separate the main effects of the factors drug and time, as well as their interaction (Drug × Time). To identify where differences occurred, orthogonal contrasts were computed between the T = 0 min values and those of the successive 5-min periods. For all comparisons, $P < 0.05$ was regarded as significant.

Results

Demographic data for the patients are shown in Table 1. There were no differences between the two groups with regard to patient age, origin of brain tumor, tumor size, shift of midline intracranial structures, or amount of peritumoral brain edema seen preoperatively on computed tomography scan.

Table 2 summarizes the baseline and final values for the measured variables during the 20-min observation period. In group 1 (isoflurane to N_2O), there was a small but statistically significant 33% increase in CSFP, despite a 3-mm Hg decrease in Pa_{CO_2}. By contrast, no change in CSFP occurred in group 2 (N_2O to isoflurane). There was no difference between the two groups with regard to baseline CSFP, nor was there a change in mean arterial pressure or heart rate in either group at any time during the study. For both groups, the end-tidal concentrations of isoflurane and N_2O were at equipotent doses (5) just before changing anesthetics (T = 0 min) and at the end of the observation period (T = 20 min). At the end of the data collection period, regardless of the anesthetic administered, CSFP was easily lowered to a target of approximately 5 mm Hg by institution of hyperventilation (Pa_{CO_2} = 20–25 mm Hg).

Figure 1 shows the changes in mean CSFP during

Table 2. Measurements at Beginning and End of 20-Minute Observation Period in the Two Study Groups

	Group 1 (Isoflurane to N_2O)		Group 2 (N_2O to isoflurane)	
	0 Min	20 Min	0 Min	20 Min
CSFP (mm Hg)	9 ± 1	12 ± 2[a]	10 ± 1	9 ± 1
MAP (mm Hg)	88 ± 5	90 ± 4	94 ± 6	87 ± 4
HR (beats/min)	75 ± 5	70 ± 5	76 ± 3	72 ± 3
Paco$_2$ (mm Hg)	37 ± 1	34 ± 1[a]	35 ± 1	36 ± 1
End-tidal isoflurane (%)	0.68 ± 0.01	0	0	0.71 ± 0.01
End-tidal N_2O (%)	0	65 ± 1	68 ± 1	0

CSFP, cerebrospinal fluid pressure; MAP, mean arterial pressure; HR, heart rate; Paco$_2$, arterial CO_2 tension.
Values are mean ± SE.
[a] $P < 0.05$ versus value at 0 min.

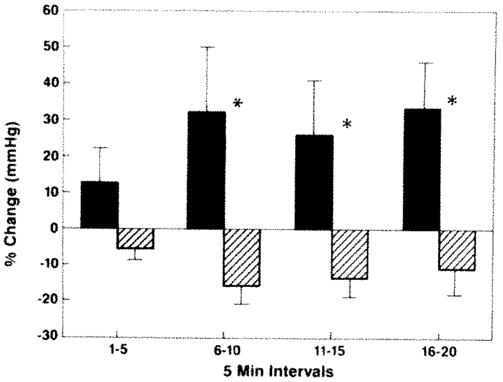

Figure 1. Changes in CSFP during the 20-min observation period for patient groups 1 (*solid bars*) and 2 (*shaded bars*). Each bar represents the average CSFP during each successive 5-min interval. Data are plotted as percent change from CSFP at time = 0 min. Values are mean ± SEM. *$P < 0.03$ vs value at time = 0 min.

sequential 5-min periods for the two anesthetic groups studied. The drug × time interaction was significant (F4,72 = 4.33; $P < 0.004$), indicating that the time-course of change in CSFP differed significantly between the two groups. Patients in group 1 sustained a gradual increase in CSFP that became statistically significant during the second 5-min interval and persisted unchanged for the remainder of the observation period. By contrast, CSFP was unchanged from baseline values in the patients in group 2. No statistically significant change in any vital sign occurred in any time period during data collection.

Discussion

Replacement of volatile anesthetics by N_2O is frequently used during general anesthesia, usually when arterial hypotension is thought to be caused by the volatile anesthetic. This study demonstrates that in patients who have compromised intracranial dynamics, replacement of isoflurane by an equipotent dose of N_2O is likely to result in an increase in CSFP, potentially resulting in compromised cerebral perfusion pressure. The increase in CSFP occurred despite a small but statistically significant decrease in Paco$_2$. Our CSFP data are in agreement with recently published studies examining the relative cerebrovascular effects of these two anesthetics at equipotent doses (3,4). Although the concentrations of N_2O and isoflurane that we studied would not produce adequate surgical anesthesia, we believed that it was important to examine the relative effects of these anesthetics at equipotent doses and that it was legitimate to use light levels of anesthesia in the absence of auditory and tactile stimuli.

Nitrous oxide increases CSFP in humans predominantly during the first 10 min of administration (1), concomitant with uptake of the anesthetic. After uptake is substantially completed, however, no further increase in CSFP would be expected to occur; indeed, this was observed in group 1 patients, who had been receiving isoflurane and were changed to N_2O. A similar time-course was reported by Archer et al. (6) for cerebral blood volume increases when they added 50% N_2O to opioid anesthesia.

It might be argued that because isoflurane is more lipid soluble than N_2O, our findings in the group 1 patients reflect the impact of both incoming N_2O and residual isoflurane in their brains and cerebral vessels, despite the fact that end-tidal isoflurane was undetectable at T = 20 min. If this were the case, it in no way detracts from our conclusion that substitution of isoflurane by N_2O may result in undesirable increases in CSFP in patients with diminished intracranial elastance.

The limitations imposed by the 20-min observation period likewise apply to group 2 patients. Thus, it is possible that the cerebral vasculature might not have achieved equilibrium with the incoming isoflurane. This would cause the brain concentration of isoflurane at the end of data collection to be less than equipotent with the 70% N_2O that preceded it. This might explain the lack of change in CSFP in group 2, which otherwise might be expected to decrease by an amount similar to the CSFP increase in group 1.

Archer et al. (6), however, noted that the effects of 2% isoflurane on cerebral blood volume were complete within 20 min of initiating administration of the anesthetic. Furthermore, the lack of any trend in CSFP in our group 2 patients at least suggests that continued uptake of 0.7% isoflurane would not have caused an increase in CSFP if the observation period had been longer.

One method for avoiding the problems of simultaneous anesthetic uptake and elimination would have been to add 1/2 MAC multiples of one agent to the other, as has been done in some recent studies of CBF (3,4). This protocol, however, is subject to possible error in interpretation, owing to the known synergistic impact of N_2O and volatile anesthetic on CBF (7). Accordingly, we chose to compare the effects of the two anesthetics at a point that we hoped would be near the end of uptake for one and elimination of the other.

Given the observed increase in CSFP that occurred in group 1 after the change from isoflurane to N_2O, it is somewhat unexpected that the CSFP at T = 0 in group 2 was not higher than that in group 1. Although this may have been the result of the somewhat lower initial $Paco_2$ in group 2 versus group 1, it also may have been due to unfortunate randomization, with patients in group 1 who were less prone to elevations in CSFP than those in group 2. Again, this in no way detracts from our observation that replacement of isoflurane by N_2O raises CSFP in patients with compromised intracranial dynamics.

The use of near normocarbia in the present study requires explanation. We decided to maintain normocarbia ($Paco_2$ = 35–40 mm Hg) throughout the protocol so that any drug-induced change in intracranial volume could be identified as a change in CSFP. Although hyperventilation to a $Paco_2$ of 20–25 mm Hg more closely resembles usual neuroanesthetic practice, the resultant reduced cerebral blood volume would have placed the patients on the horizontal portion of their CSFP-intracranial volume relationship, thus obscuring any changes induced by the anesthetics under investigation. We speculate that we were able to measure drug-induced changes in CSFP in these patients with brain tumors because relative normocarbia placed their CSFP-intracranial volume relationship close to the "knee" of its hyperbolic curve. We believe that it is likely that if our patients had had overt intracranial hypertension at T = 0, we would have observed far greater increases in CSFP when isoflurane anesthesia was changed to N_2O.

Experimental support for this speculation is provided by Archer et al. (6) who noted that the addition of 50% N_2O to an opioid anesthetic during normocapnia caused an 11% increase in cerebral blood volume, whereas there was no increase when $Paco_2$ was 20–30 mm Hg. Similarly, when 2% isoflurane was added to the same opioid anesthetic at normocarbia, there was a 31% increase in cerebral blood volume, whereas there was only a 15% increase in cerebral blood volume at $Paco_2$ = 20–30 mm Hg.

Clinical studies also support our speculation: 66% N_2O has long been known to increase CBF (8) and has been associated with large increases in CSFP, even in hyperventilated patients who had compromised intracranial compliance (1). By contrast, the CBF effects of 1.0% isoflurane (added to 60% N_2O/fentanyl anesthesia) have been found to be minimal in patients with brain tumors (9). When an increase in CSFP has been reported during isoflurane anesthesia, it was in the presence of normocarbia (10) or during modest hyperventilation in patients who had computed tomography evidence of seriously compromised intracranial compliance (2).

An additional advantage to performing this study at near normocarbia is that it avoids the confounding influence of anesthetic-induced differences in cerebrovascular responses to hypocapnia. Drummond and Todd (11) have shown in cats that there is a more profound reduction in CBF during the change from normocapnia to hypocapnia with isoflurane than with N_2O anesthesia. If this were true in humans, then one might anticipate that hyperventilation would be less effective in reducing CSFP during N_2O anesthesia than during isoflurane anesthesia.

Although we found that hyperventilation instituted after T = 20 min resulted in prompt reduction of CSFP to approximately 5 mm Hg in both groups of patients, we did not attempt to compare the impact of the different anesthetics on CSFP response to hypocapnia. The decreases in CSFP, however, were consistent with those observed in animal studies using N_2O (6) and in human studies using isoflurane (10).

In summary, we found that in normocapnic patients who have compromised intracranial dynamics, changing from isoflurane to an equipotent concentration of N_2O resulted in increases in CSFP. Although this change in anesthetic is frequently used clinically, we conclude that it may be problematic in patients at risk for intracranial hypertension.

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Effect of Partial Neuromuscular Blockade on Intraoperative Electromyography in Patients Undergoing Resection of Acoustic Neuromas

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Intraoperative electromyographic monitoring of the facial nerve during acoustic neuroma excision provides early detection of nerve injury and improved outcome. To determine whether a useful level of peripheral neuromuscular blockade could be achieved without compromise of facial electromyographic monitoring, we studied 10 patients undergoing resection of acoustic neuroma. Facial nerve monitoring was accomplished by placement of wire electrodes in the orbicularis oris, orbicularis occuli, and mentalis muscles. Peripheral neuromuscular blockade was assessed by recording unprocessed hypothenar compound muscle action potentials (CMAPs). After induction of anesthesia, an infusion of atracurium (1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$) accompanied by a bolus dose of 50 $\mu g/kg$ was administered. The infusion was then increased in increments of 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ until a 50% reduction in hypothenar single-twitch CMAP was obtained. Facial nerve function was continuously monitored by comparison of facial CMAPs produced by stimulation of the nerve proximal and distal to the tumor bed. The mean (±SD) infusion rate of atracurium was 2.55 ± 0.75 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Decrements in facial nerve CMAPs were detected in 6 of 10 patients, and all demonstrated moderate to severe facial nerve dysfunction. In no patient was an unexpected deficit present postoperatively. Moderate degrees of peripheral neuromuscular blockade can be achieved without compromising facial nerve electromyographic monitoring.

(Anesth Analg 1992;75:729–33)

Acoustic neuromas are the most common benign tumors of the posterior cranial fossa. Cranial nerve involvement with acoustic neuromas is common (1–7). Auditory nerve impairment is present in almost all cases. In addition, nerve conduction studies before any surgical procedures reveal electrical evidence of neuropathy of the facial nerve in 83% of patients (1). The close proximity of the facial auditory nerves within the internal auditory canal accounts for the combined cranial nerve involvement commonly seen with acoustic neuromas (Figure 1). Intraoperative electromyographic (EMG) monitoring of the facial nerve during acoustic neuroma resection allows early detection of surgical stimulation and reduces nerve dysfunction postoperatively. The gains achieved by advances in monitoring technology, however, may place additional constraints on the anesthetic management of these patients. Neuromuscular blocking agents have been avoided for these types of procedures to exclude any compromise of facial EMG monitoring capability. Simultaneous monitoring of brainstem auditory evoked potentials may limit the use of volatile anesthetic agents.

The retrosigmoid approach to acoustic neuroma resection maximizes facial nerve preservation. However, the additional hazards of posterior fossa exploration are encountered. Delicate microsurgical resection of these tumors demands absolute immobility of the patient. Close proximity of the trigeminal nerve and brainstem structures may result in unintentional stimulation of these structures, producing rapid motor or hemodynamic reflexes. Ensuring immobility in the lightly anesthetized, unparalyzed patient under these circumstances may be difficult. The intent of this report is to examine the possibility of introducing controlled levels of neuromuscular blockade while preserving the ability to adequately monitor facial nerve EMGs.

Methods

Ten patients undergoing acoustic neuroma resection with standard facial nerve EMG monitoring were studied. The protocol was approved by the Mayo Institutional Review Board, and written, informed

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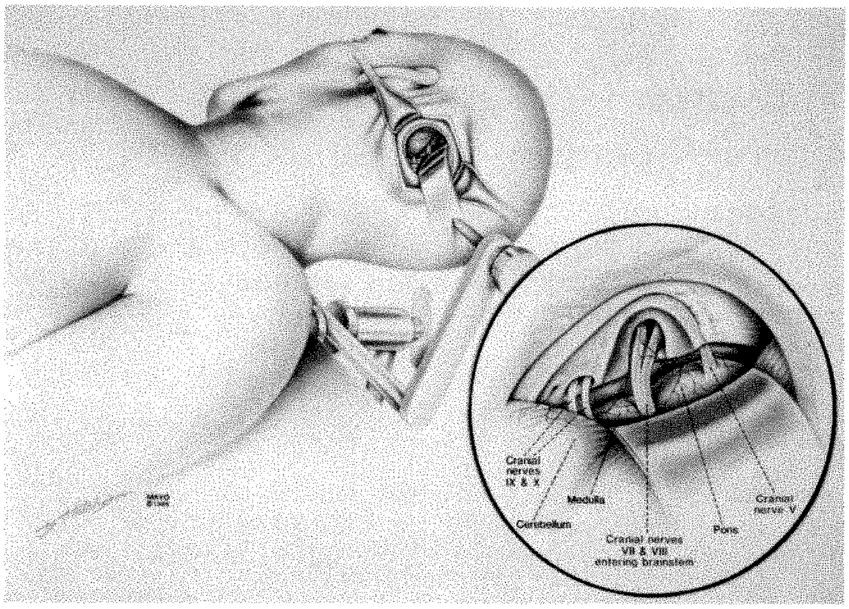

Figure 1. Diagram of the operative field during acoustic neuroma resection demonstrating the proximity of the auditory and facial nerves. (Modified with permission from Harner SG, Daube JR, Ebersold MJ, Beatty CW. Improved preservation of facial nerve function with use of electrical monitoring during removal of acoustic neuromas. Mayo Clin Proc 1987;62: 92–102.)

consent was obtained from all patients. Preoperative electrophysiologic studies of facial nerve function included EMG and nerve conduction studies, and these results were evaluated by a staff electromyographer. In all patients, a posterior fossa (retrosigmoid) approach was used. All patients were monitored by electrocardiography, pulse oximetry, and esophageal temperature probe. An intraarterial catheter was inserted in the radial artery and zeroed at midcardiac level. Expired gas concentrations were monitored by mass spectroscopy.

Intraoperative monitoring of facial nerve function consisted of two components. First, visual and auditory monitoring of facial nerve EMG activity was used during surgical exposure. Second, compound muscle action potentials (CMAPs) were recorded in response to direct stimulation of the facial nerve by the surgeon after exposure of the nerve.

An electromyographer monitored intraoperative facial nerve function continuously during the operative procedure. Electromyographic monitoring was accomplished by preoperative placement of wire electrodes in muscles innervated by the facial nerve. Insulated nickel and chromium wire electrodes (0.03 mm) were inserted into the orbicularis oris, orbicularis occuli, and mentalis muscles, with a reference electrode placed within the same muscle. The wires were connected to preamplifiers attached to the operating table by probit connectors. Recordings were made at 200-μV gain, with 32-Hz low and 16-kHz high filter settings. Oscilloscope sweep speed was 10 ms/cm. A filter switch on the cautery pedal suppressed cautery noise. Electromyographic activity was recorded continuously on magnetic tape as well as viewed on the oscilloscope. In addition, the signal was played over an audio amplifier and loudspeaker for continuous auditory monitoring by the surgeon.

The CMAPs of the facial nerve were produced by direct constant-voltage stimulation of the nerve in the surgical field. Square-wave pulses (0.05 ms, 10–50 V) via a bipolar electrode were delivered to the muscle through a silver-cadmium alloy wire. The CMAPs were recorded by the wire electrodes in the muscle or from 8-mm tin disks applied with collodion over the nasalis and mentalis muscles. Baseline responses were recorded before induction of anesthesia. Responses were tape-recorded and photographed on direct writing paper. Neuronal damage was determined by the relative amplitudes of the CMAPs at the most proximal and distal stimulation sites.

Peripheral neuromuscular blockade was monitored by recording unprocessed hypothenar CMAPs elicited by stimulation of the ulnar nerve at the wrist. Wire electrodes were inserted along the ulnar nerve, and surface tin disk electrodes were placed over the belly of the hypothenar muscles and secured with collodion to record the CMAPs. The peak-to-peak changes were recorded on photosensitive paper for measurement.

Anesthesia was induced with thiopental (3–5 mg/kg) and fentanyl (5–10 μg/kg). Tracheal intubation was facilitated with atracurium (0.4 mg/kg). Anesthesia was supplemented with a continuous infusion of fentanyl (1–2 $\mu g \cdot kg^{-1} \cdot h^{-1}$). Mechanical ventilation was initiated immediately after endotracheal intubation with 50% nitrous oxide in oxygen, and controlled hyperventilation was begun when clinically indicated. Isoflurane was introduced as needed and was maintained below 1% end-expired concentration.

Hypothenar muscle EMGs were recorded after ulnar nerve stimulation at 2 and 20 Hz for 2–3 s, with 0.2-ms duration at 15-min intervals until complete recovery was observed consistent with preinduction baseline values. After recovery of neuromuscular function and observation of the return of neurotonic discharges from the facial nerve, the atracurium infusion was initiated. An initial infusion rate of 1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ preceded by a bolus dose of 50 μg/kg was administered in an effort to rapidly reach a stable level of neuromuscular blockade. At 10-min intervals, we administered a bolus dose of 25 μg/kg of atracurium and increased the infusion in increments of 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Once a 50% decrement of the hypothenar single-twitch CMAP was obtained, the infusion rate was fixed and the level of peripheral neuromuscular blockade was evaluated every 10 min. Adjustments to the infusion rate were made as necessary to maintain a 50% decrement in the hypothenar CMAP amplitude.

During critical periods in the operative procedure, the facial nerve was directly stimulated with a bipolar electrode by the surgeon. The facial CMAPs generated were used as a guide for further dissection and as a gauge of intraoperative preservation of facial nerve function. If at any time the electromyographer determined that the quality of monitoring was compromised, the infusion would be decreased or terminated as needed.

After the head dressing had been applied, the anesthetic was terminated. Grip strength, positive expiratory pressure, negative inspiratory force, tidal volume, and head lift were evaluated to clinically assess the presence of muscle weakness. Residual neuromuscular blockade was antagonized with intravenous edrophonium (0.5 mg/kg) and atropine (7 μg/kg). Extubation of the trachea was performed when the patient was awake and following commands and neuromuscular blockade had been effectively antagonized. Postoperatively, facial nerve function was evaluated by a neurologist and the neurosurgeon.

Results

Preoperatively, all 10 patients demonstrated clinically normal facial nerve function. Five patients had large tumors (>2.5 cm), and five had medium-sized tumors (1.0–2.5 cm). Electromyographic analysis before surgery revealed normal function in four patients, mild facial nerve neuropathy in five patients, and a moderate degree of neuropathy in one patient.

Adequate intraoperative facial nerve monitoring was accomplished in all patients in the presence of moderate degrees of peripheral neuromuscular blockade. The maximal decrement in facial nerve EMG amplitude observed during 50% reduction of hypothenar twitch height was 6% from control. In six patients, impaired facial nerve function was detected by intraoperative facial EMG analysis. Impaired facial nerve function was indicated by loss or reduction of facial CMAPs after direct intraoperative stimulation of the nerve proximal to the tumor with preservation of facial CMAP following stimulation of the facial nerve distal to the tumor bed (Figure 2). Two patients demonstrated a reduction in the proximal, relative to the distal, CMAP, whereas four patients experienced complete loss of the proximal facial nerve CMAP. All six patients had moderate to severe facial nerve dysfunction postoperatively. In no patient was an unexpected deficit present postoperatively.

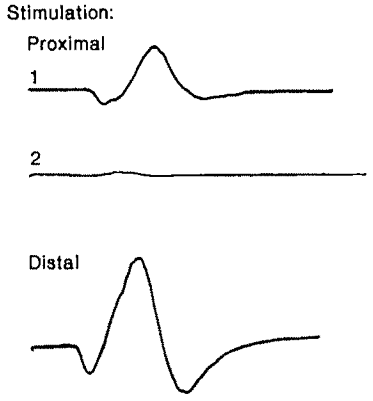

Figure 2. Facial EMG demonstrating (*1*) initial proximal stimulation; (*2*) loss of proximal EMG after acoustic neuroma resection and distal stimulation.

Stable levels of neuromuscular blockade were readily achieved and maintained in all patients. In all patients, the hypothenar CMAPs were reduced to 50% of control, whereas facial nerve CMAPs were spared, and continuous monitoring of facial nerve function was possible. To achieve a 50% decrement in first-twitch amplitude, the mean maintenance infusion rate was 2.55 ± 0.75 (SD) $\mu g \cdot kg^{-1} \cdot min^{-1}$, and the mean total bolus dose was 118 ± 32 μg/kg. The mean duration of atracurium infusion was 162.7 ± 39.8 min. It was not necessary to decrease or discontinue the atracurium infusion in any patient. After emergence from anesthesia, but before antagonism of neuromuscular blockade, all patients had muscle weakness manifested by decreased grip strength and impaired ventilatory mechanics. Muscle weakness resolved rapidly in all patients after administration of edrophonium and atropine.

Discussion

In patients undergoing acoustic neuroma resection, intraoperative EMG monitoring of the facial nerve has resulted in improved preservation of facial nerve function postoperatively (1).

The anesthetic management of these patients should provide hemodynamic stability while preserving an optimal environment for facial EMG and brainstem auditory evoked potential monitoring. To preserve facial nerve EMG monitoring, neuromuscular blockade has been avoided during resection of acoustic neuromas (1,2,5,6). The results of this study demonstrate the ability to achieve moderate levels of peripheral neuromuscular blockade while preserving facial EMG monitoring by careful titration of an intermediate-acting, nondepolarizing muscle relaxant.

The only previous evaluation of the effects of neuromuscular blockade on facial nerve monitoring during acoustic neuroma resection differed methodologically from the present study. Ho et al. (8) used mechanomyographic assessment of facial and hypothenar function by means of accelerometery. A single large bolus dose of atracurium was administered, and recovery of facial and hypothenar responses were compared. No patients demonstrated facial nerve dysfunction postoperatively, preventing an evaluation of the potential for false-negative results. In addition, because EMG monitoring was not used and stable levels of neuromuscular blockade were not achieved, the impact of partial blockade on neurotonic discharges could not be evaluated. A strong correlation has been demonstrated between the intensity of neurotonic discharges and the extent of surgical trespass and postoperative facial nerve function (1).

The simple infusion protocol used in this study produced moderate levels of neuromuscular blockade while preserving facial nerve EMG potentials. Ease of administration, stability in normal saline solution, and rapid titratability and reversibility make atracurium an attractive choice for these purposes (9). Electromyographic monitoring of neuromuscular blockade is less sensitive to depression than mechanomyographic methods, and EMG values exceed corresponding mechanomyographic values by approximately 15% (10). Thus, a 50% decrement in the twitch height of the EMG correlates with a 65% reduction in twitch height measured by mechanomyographic means. This correlates with a receptor occupancy of 80%–85% (11). Although this level of blockade does not ensure complete paralysis, neuromuscular transmission is significantly reduced. Adequate surgical relaxation may occur with 55%–60% EMG twitch height reduction (10), levels approximated in this study.

Two of the six patients experiencing facial nerve EMG decrements demonstrated a partial reduction in amplitude without complete loss of the EMG signal. Partial preservation of facial nerve electrical function correlates well with long-term recovery of facial nerve function (12). The two patients in this study subsequently recovered facial nerve function. Thus, partial peripheral neuromuscular blockade did not impair the capacity of facial nerve EMG monitoring to detect facial nerve injury that was potentially reversible. In addition, the controlled level of neuromuscular blockade allowed rapid and predictable reversal of blockade at the end of the procedure. Four patients experienced complete loss of facial nerve CMAP during surgery, and all four experienced severe weakness or total facial nerve paralysis. All four patients had large tumors (>2.5 cm). These results are consistent with those reported by Moffat et al. (13) documenting a 79% rate of facial nerve division with large tumors. Previous reports may not have differentiated between anatomic and functional preservation of the facial nerve, thus implying a falsely low rate of facial nerve injury. This high-risk cohort permitted us to document for the first time the capacity to detect facial nerve injury during moderate degrees of peripheral neuromuscular blockade.

Intraoperative anesthetic management of patients undergoing acoustic neuroma resection is made more difficult by marked variation in the level of surgical stimulation due to intraoperative manipulation of the cranial nerves. The goals of anesthetic management include maintenance of hemodynamic stability while preserving an optimal environment for monitoring of cranial nerve function. Controlled infusion of atracurium titrated to a 50% reduction in hypothenar EMG twitch height did not impair the capacity of facial nerve EMG monitoring to detect facial nerve injury. The capacity to safely monitor facial nerve EMG activity during partial neuromuscular blockade has thus been demonstrated.

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Comparison Among Intrathecal Fentanyl, Meperidine, and Sufentanil for Labor Analgesia

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This study compared the analgesic efficacy of intermittent injections of intrathecal fentanyl (10 μg), meperidine (10 mg), or sufentanil (5 μg) administered to 65 parturients during the first stage of labor. The groups did not differ in onset or duration of effective analgesia. The meperidine group, however, had significantly lower pain scores once cervical dilation progressed beyond 6 cm. Side effects included mild pruritus and nausea. After intrathecal drug injection, variable decelerations of the fetal heart rate increased in the fentanyl and meperidine groups. All neonates had a 5-min Apgar score of 7 or more. We conclude that intermittent intrathecal injections of fentanyl, meperidine, or sufentanil can provide adequate first-stage labor analgesia. Meperidine appears to provide more reliable analgesia as the first stage of labor progresses.

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Intrathecal opioids relieve labor pain (1–3) with few of the systemic side effects associated with epidural injection of opioids and local anesthetics (4). Additionally, intrathecal opioids appear to have no effect on the fetus during either the intrapartum or immediate postpartum period (1–3).

Several studies describe the administration of intrathecal morphine during parturition (1–3,5). Morphine, a highly ionized, water-soluble opioid, produces analgesia of long duration but slow onset. This slow onset, plus a high incidence of side effects, such as nausea, vomiting, pruritus, and the potential for delayed respiratory depression, limit the usefulness of intrathecal morphine for labor analgesia. Intrathecal injection of a more lipid-soluble opioid leads to rapid relief of labor pain with fewer side effects, but the duration of analgesia is relatively short (6,7). Thus, in most patients, a single intrathecal injection of a lipid-soluble opioid is insufficient to produce analgesia for the entire duration of labor.

Recently developed small-gauge spinal catheters allow repeated intrathecal opioid injection (8). These catheters have been used successfully to provide labor analgesia by allowing administration of multiple intrathecal doses of a lipid-soluble opioid, such as fentanyl, meperidine, or sufentanil (9–13). Because no study has systematically compared these three drugs, we examined their analgesic efficacy, duration of action, and hemodynamic and other side effects during the first stage of labor.

Methods

Healthy women at term of pregnancy gave informed consent to participate in this prospective, double-blind study, approved by our Institutional Review Board. All patients were in active labor, with cervical dilation between 2 and 7 cm. Fetuses presented by the vertex, and fetal heart rate (FHR) traces appeared normal. Women with moderate or severe pregnancy-induced hypertension or multiple gestations were excluded from the study. Monitoring included the use of a cardiotocodynamometer and a noninvasive maternal blood pressure device. Using either a 22-gauge Levi point needle ($n = 5$) or a 22-gauge ramped Sprotte needle ($n = 60$) (Figure 1), we placed a 28-gauge polyurethane spinal catheter (Preferred Medical Products) at the L2-3 or L3-4 interspace via a paramedian approach. After catheter insertion, patients assumed a semirecumbent position with left uterine displacement, and a 250-mL intravenous bolus dose of a balanced salt solution was infused. Patients remained at bed rest for the remainder of their labor. A 1-mL solution containing fentanyl (10 μg), meperidine (10 mg), or sufentanil (5 μg) in preservative-free normal saline (as determined by a

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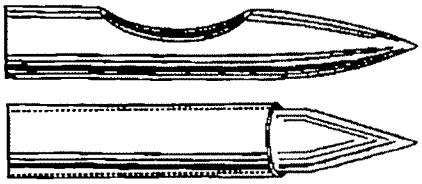

Figure 1. The Sprotte needle (*top*) compared with the Levi point needle (*bottom*). The Levi needle stylet contains the needle point. After removal of the stylet, the catheter passes through the shaft of the needle.

table of random numbers) was then injected into the intrathecal space. These doses were based on preliminary unpublished work using this spinal technique. If analgesia was inadequate after 15 min, a second dose of the same study solution was injected. After 30 min, if analgesia was still inadequate, intrathecal bupivacaine (2.5 mg) (1 mL 0.25%) was administered. After bupivacaine injection, a lack of sensory block was assumed to indicate that the catheter tip was not in the intrathecal space, in which case the catheter was removed and the patient excluded from further study. As labor progressed and the patient requested additional analgesia, this protocol was repeated.

Before intrathecal injection and every 5 min thereafter for up to 30 min, patients rated their pain, nausea, and pruritus on unmarked 10-cm horizontal visual analogue scales (VAS). They continued to rate these variables every 30 min until they requested additional pain relief. Concurrently, we measured blood pressure (BP) and evaluated sensory (alcohol pad) and motor (Bromage scale) blocks. These determinations were also made immediately before and 15 min after each reinjection. Obstetricians measured cervical dilation as clinically indicated. Termination of the study occurred when the patient reached 10-cm cervical dilation or required bupivacaine to achieve adequate analgesia. We defined the duration of effective opioid analgesia as the time from initial study drug injection until termination of the study. Once a patient was given bupivacaine, she received only local anesthetic until delivery. We recorded the time and type of delivery (spontaneous vaginal, instrumented vaginal, or cesarean section).

We collected FHR-uterine activity tracings from 10 min before until 20 min after injection of the study drug. The perinatologist interpreting the data was unaware of which study solution was being administered. Tracing analysis included baseline FHR, number of accelerations per 20 min, short-term variability, decelerations (variable, late, and early), and number of uterine contractions per 20 min. We defined adequate short-term FHR variability as ≥10 beats/min and decreased short-term variability as <10 beats/min.

Obstetricians collected arterial and venous umbilical cord blood samples at their discretion. We recorded the Apgar scores of all neonates.

We inquired about the presence and severity of spinal headache at 24 h after delivery. The patients rated their headache as none, mild, moderate, or severe. A headache was considered mild if it did not limit the patient's activity and moderate if it did. An incapacitating headache was rated as severe.

To control for the unpredictable duration of labor, we evaluated the pain VAS versus the cervical dilation. In each patient, we analyzed the lowest pain score achieved with intrathecal opioids alone for each cervical dilation. For any cervical dilation without a simultaneously recorded pain score, we used the pain score from the last measured cervical dilation that had a concurrently reported pain score. If intrathecal opioids no longer provided adequate pain relief and the parturient required bupivacaine for labor analgesia, we recorded the last pain score reported with intrathecal opioids alone (usually >8) for the remaining cervical dilations. For patients who delivered by cesarean section, we stopped recording the pain score at the last known cervical dilation before surgery.

We used one-way analysis of variance or the Kruskal-Wallis test where appropriate for the comparison of demographic data, time to delivery, method of delivery, incidence of headache, number of bolus doses to make the patient comfortable, fetal umbilical cord blood gas tensions, Apgar scores, and FHR data. We applied analysis of variance for repeated measures to BP, pain, nausea, and pruritus VAS, sensory blockade data, and cervical dilation versus pain VAS. To compare the duration of analgesia after the first dose of opioid and the total duration of effective opioid analgesia, we used product limit survival analysis and Gehan Wilcoxon's test. For all statistical analysis, we considered results at $P < 0.05$ significant.

Results

Sixty-five patients consented to participate in this study. We excluded four patients from the study, because the spinal catheter failed secondary to misplacement or dislodgment. One patient in the sufentanil group experienced a severe deterioration in the FHR tracing and proceeded to emergency cesarean section 10 min after her initial dose. At delivery, the obstetrician noted that the umbilical cord was wrapped twice around the neck of the fetus. This patient is included only in baseline statistical evaluation; however, we enrolled an additional sufentanil-group patient to achieve an equal number of patients who completed the study ($n = 20$) in each group.

Table 1. Patient Demographics

	Fentanyl (n = 20)	Meperidine (n = 20)	Sufentanil (n = 20)
Age (yr)	27 ± 7	26 ± 6	28 ± 7
Height (cm)	163 ± 6	162 ± 5	163 ± 6
Weight (kg)	76 ± 10	80 ± 15	75 ± 11
Parity (%)			
0	55	75	71
1	35	20	24
>1	10	5	5
Baseline cervical dilation (cm)	4.3 ± 1.0	3.8 ± 1.3	3.5 ± 1.3
Time to delivery (min)	328 ± 211	302 ± 188	342 ± 193
Method of delivery (%)			
Spontaneous vaginal	55	55	38
Instrumented	35	25	28
Cesarean section	10	20	33
Headache (%)			
None	90	95	90
Mild	5	5	5
Moderate	0	0	5
Severe	5	0	0

Data are mean ± SD or percentages. No significant differences among groups.

Table 2. Opioid Characteristics

	Fentanyl	Meperidine	Sufentanil
Avg 1st dose[a]	15.5 ± 5.1 μg	10.2 ± 2.2 mg	6.5 ± 2.4 μg
Duration of 1st dose (min)			
Median	70	98.7	95
Mean ± SD	81.6 ± 8.9	103.5 ± 10.6	103.9 ± 8.7
Range	0–150	35–205	0–210
Duration of effective opioid analgesia (min)			
Median	227.1	301	250.7
Mean ± SD	216.9 ± 30.9	267.5 ± 23.9	267.5 ± 31.9
Range[b]	0–380	35–710	0–545

Avg, average.

[a] To make patient comfortable; mean ± SD.

[b] Potential range of analgesia unknown because some patients delivered without receiving intrathecal local anesthetic. No significant differences among the groups.

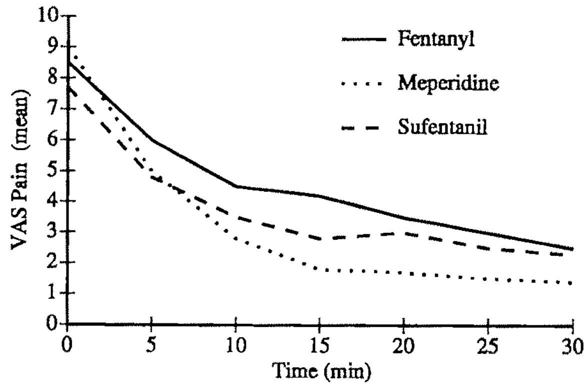

Figure 2. Pain visual analogue scale (VAS) for each opioid during the first 30 min after injection.

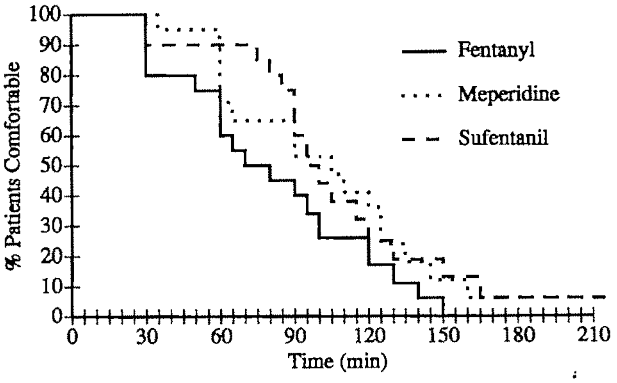

Figure 3. Step graph depicting the duration of analgesia provided by the first opioid injection. The graph steps down when patients requested additional analgesia or received bupivacaine for opioid failure. Some patients in the meperidine and sufentanil groups delivered without requesting supplemental analgesia; therefore, these lines do not intersect with the x-axis.

The groups did not differ in demographic attributes, time to delivery, method of delivery, or cervical dilation at baseline (Table 1). The average first dose to make a patient comfortable, the duration of the first dose of opioid analgesia, and the duration of effective opioid analgesia for each group are presented in Table 2. The groups did not differ in onset of analgesia (Figure 2), duration of the first dose of opioid analgesia (Figure 3), or duration of effective opioid analgesia (Figure 4). Two fentanyl-, zero meperidine-, and two sufentanil-group patients had inadequate analgesia at 30 min and required bupivacaine. Meperidine-group patients had significantly lower VAS pain scores once cervical dilation reached 6 cm and beyond (Figure 5). The percent of patients in each group who underwent vaginal delivery without intrathecal bupivacaine was 33% (fentanyl), 75% (meperidine), and 36% (sufentanil).

Patients in each group noted a similar small but significant increase in pruritus over time. Meperidine-group patients experienced more nausea, yet nausea scores in all groups were very low (Figure 6). All three groups had a slight decrease in BP from baseline (none <95 mm Hg systolic or >15%). There was transient sensory change in temperature in each group. No patient developed a detectable motor block.

We noted no significant intergroup differences in the FHR variables (Table 3). In both the fentanyl and meperidine groups, there was an increase in the number of variable decelerations after intrathecal drug injection. There was no change in the incidence of early or late decelerations (Table 3). Although

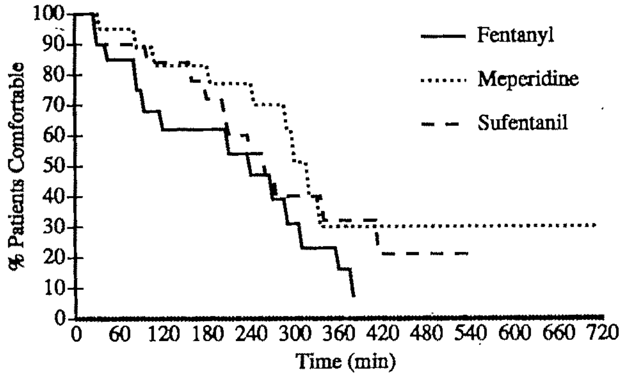

Figure 4. Step graph depicting the duration of effective opioid analgesia. The graph steps down when patients required injection of bupivacaine for adequate pain relief. The denominator changes when patients received bupivacaine for delivery. Some patients in each opioid group delivered without requiring bupivacaine analgesia; therefore, these lines do not intersect with the x-axis.

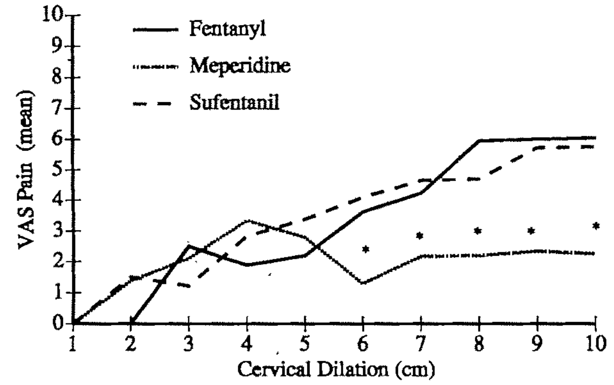

Figure 5. Pain visual analogue scale (VAS) versus cervical dilation. *$P < 0.05$ for meperidine versus fentanyl and sufentanil.

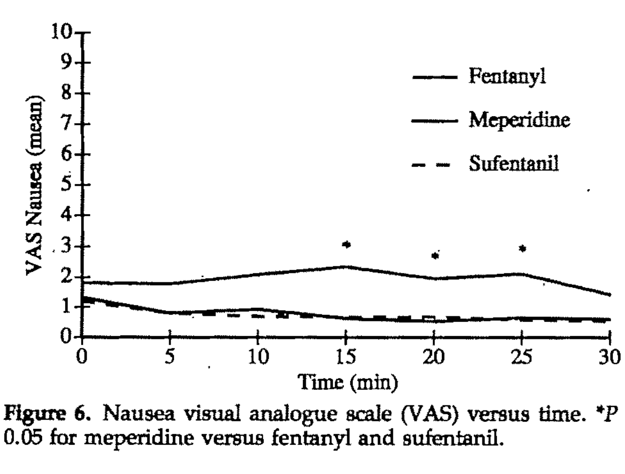

Figure 6. Nausea visual analogue scale (VAS) versus time. *$P < 0.05$ for meperidine versus fentanyl and sufentanil.

drawn selectively by the obstetrician, there were no intergroup differences in the umbilical cord blood gas tensions. No neonate had a 5-min Apgar score of <7.

The incidence of postdural puncture headache was 8.2%. Postdural puncture headache did not correlate with the opioid (Table 1) but did correlate with the type of needle used. We performed dural puncture with a 22-gauge Levi point needle in five parturients. Postdural puncture headache occurred in four of them. Of the remaining 56 patients (22-gauge ramped Sprotte needle), 1 developed a headache. In the Levi point needle group, one patient experienced a severe headache, requiring an epidural blood patch. The four other parturients with postdural puncture headache responded to conservative therapy.

Discussion

Several investigators have recently described the intrathecal use of the more lipid-soluble opioids for labor analgesia. Although the effect is not as long lasting as morphine analgesia, the reported incidence, duration, and severity of side effects are also less (6,7,10–14).

The present study examined the efficacy of intermittent intrathecal opioid injection in providing pain relief for the first stage of labor. Initially, intrathecal fentanyl, sufentanil, and meperidine produced similar analgesia with minimal side effects. After cervical dilation exceeded 6 cm, meperidine-group patients consistently reported lower VAS pain scores.

As labor advances, the nature of pain becomes increasingly somatic. Although all three opioids studied possess local anesthetic activity in vitro (15,16), only meperidine can function as a spinal anesthetic in clinical practice (17). This local anesthetic action may explain the greater degree of patient comfort in the meperidine group.

An alternative explanation for the increasing pain scores throughout labor is the occurrence of tachyphylaxis. We noted that in many patients, the duration of a given dose of opioid decreased with each successive injection. This phenomenon has been described in another study of intrathecal fentanyl used for labor analgesia (14). It is extremely difficult in a clinical study to differentiate between the changing nature of labor pain and tachyphylaxis. Either occurrence, or a combination of both, could explain the clinical results.

All three opioids caused minimal side effects. Although intrathecal meperidine was associated with more nausea than the other two agents, episodes were brief. Intrathecal administration of all three opioids did not produce any significant decreases in BP. There were no instances of motor block, but discernible sensory changes, consistent with the local anesthetic properties, occurred in all groups. It appears that short-acting spinal opioids offer a safe alternative to epidural local anesthetics, especially in patients whose hemodynamic stability is of particular concern.

Table 3. Fetal Heart Rate

	Fentanyl group (beats/min)		Meperidine group (beats/min)		Sufentanil group (beats/min)	
	Predose	Postdose	Predose	Postdose	Predose	Postdose
Baseline	133 ± 7	131 ± 7	139 ± 11	139 ± 12	141 ± 12	143 ± 13
No. of accelerations/20 min	1 ± 1	2 ± 1	2 ± 1	2 ± 2	2 ± 2	1 ± 2
Short-term variability						
Adequate	9	11	13	14	14	12
Decreased	6	4	2	1	3	5
Deceleration						
Variable	4	10[a]	3	8[a]	6	9
Late	0	2	1	2	0	4
Early	0	2	0	1	3	1
No. of uterine contractions/20 min	5 ± 3	6 ± 3	5 ± 2	6 ± 2	5 ± 2	5 ± 2

Values expressed as mean ± SD or number of patients.
[a] $P < 0.05$ compared with predose.

Evaluation of the FHR tracings before and after intrathecal opioid injections, as well as determination of acid-base status and Apgar scores, revealed no intergroup differences. As shown in Table 3, in the fentanyl and meperidine groups, the number of fetuses with variable decelerations postdose increased significantly. Yet, without significant changes in the baseline FHR, short-term variability, or number of fetuses manifesting late decelerations, it is unlikely that this single finding is of clinical significance.

There are no studies delineating intrathecal opioid potency ratios in parturients. Systemic opioid potencies, which correlate directly with opioid lipophilicity, reflect the need for the drug to cross the blood-brain barrier to gain access to the receptor site. Because intrathecally injected drugs bypass the blood-brain barrier, systemic opioid potencies do not predict intrathecal potency. In an animal model, intrathecal drug potency is inversely related to lipid solubility (18). It is possible that nonspecific binding of the highly lipid-soluble drugs by perineural tissue leaves less drug available for opioid receptor binding (18).

The design of the present study considered patient comfort as the endpoint for further opioid administration. Although we cannot accurately comment on potency ratios, our data appear to agree with the finding that intrathecal potency varies inversely with lipid solubility. Sufentanil (octanol/water partition coefficient 1778) is considered 10 times as potent as fentanyl (octanol/water partition coefficient 813) when systematically administered (19). In contrast, our data suggest that after intrathecal injection, sufentanil is only twice as potent as fentanyl.

Postdural puncture headache occurs frequently in parturients. In this study, we found no correlation between headache and opioid administered. There was an 80% incidence of postdural puncture headache with the use of the 22-gauge Levi point needle, in contrast to the 1.7% incidence with the 22-gauge Sprotte needle. Because a large-gauge spinal needle is necessary to thread a catheter, it is important to select a needle with an atraumatic bevel, particularly for use during parturition.

Currently, there is much concern about cauda equina syndrome and the continuous spinal technique. All cases reported to date were associated with hyperbaric local anesthetic solutions (20). In this study, we administered local anesthetics only if the patient perceived the opioid analgesia as inadequate, or at the request of the obstetrician, or for cesarean section anesthesia. If analgesia was not achieved with a specific dose range of local anesthetic, we assumed that the spinal catheter was not functioning and removed it. The following doses were used: during labor, a total of 5 mg of 0.25% bupivacaine; for vaginal delivery, a total of 7.5 mg of 0.75% bupivacaine with 8.25% dextrose; for cesarean section, 15 mg of 0.75% bupivacaine with 8.25% dextrose. When using hyperbaric bupivacaine, a sensory block of inadequate dermatomal spread was treated by modifying the patient's position or adding a small dose of isobaric or hypobaric local anesthetic. After this protocol, no patient experienced adverse neurologic sequelae.

In conclusion, we have shown that an intermittent injection spinal technique with fentanyl, meperidine, or sufentanil provides adequate first-stage labor analgesia. There is a small incidence of mild side effects associated with this technique. Meperidine may have advantages over the other two opioids, because it provides more reliable analgesia as the first stage of labor progresses.

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Epidural Patient-Controlled Analgesia: Influence of Bupivacaine and Hydromorphone Basal Infusion on Pain Control After Cesarean Delivery

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Epidural administration of hydromorphone was evaluated using a patient-controlled analgesia (PCA) delivery system in 170 healthy women undergoing elective cesarean delivery with epidural bupivacaine who were randomly assigned to one of four epidural PCA treatment groups: group I, hydromorphone alone by bolus administration; group II, hydromorphone, with a continuous (basal) infusion; group III, hydromorphone in combination with 0.08% bupivacaine by bolus administration; or group IV, hydromorphone and bupivacaine, with a concurrent infusion of both drugs. Patients in group I required significantly less opioid medication (2.1 ± 1.1 mg [mean ± SD]) during the first 24 h than patients in group II (3.3 ± 1.3 mg). Similarly, patients in group III self-administered significantly less hydromorphone (2.0 ± 1.0 mg) and bupivacaine (23.3 ± 11.4 mg) during the first 24 h of PCA therapy, compared with patients in group IV (hydromorphone [2.7 ± 1.1 mg] and bupivacaine [31.5 ± 11.6 mg]). The concomitant use of a local anesthetic or basal opioid infusion with hydromorphone via epidural PCA did not decrease the number of PCA demands or delivered doses. In addition, patients in all four groups had similar pain, sedation, discomfort, fatigue, and anxiety scores. The frequency of awakening at night to self-administer analgesic medication was not decreased when a basal infusion was used. Although only 5% of patients receiving hydromorphone alone complained of nausea, 25% of the patients receiving the opioid-local anesthetic combination (group III) reported PCA-related nausea ($P < 0.05$). Although the overall incidence of pruritus did not differ among treatment groups (55%–72%), 42% of patients in group IV required antipruritic therapy compared with 22% in group I ($P < 0.05$). Minimal hemoglobin oxygen saturation values at night were 94% (±2%) in all four groups. Persistent lower extremity paresthesias were noted in 22% of patients receiving the opioid-local anesthetic infusion (group IV), with 20% requiring discontinuation of the infusion secondary to difficulty ambulating. In the opioid-local anesthetic combination (vs opioid alone) group, significantly more patients required recatheterization, owing to urinary retention. Times to recovery of bowel function, ambulation, resumption of a solid diet, discontinuation of PCA therapy, and hospital discharge were similar in all four groups. In conclusion, the efficacy of epidural PCA with hydromorphone was not improved by adding 0.08% bupivacaine or a basal hydromorphone infusion (0.0375 mg/h) after cesarean delivery.

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Epidural administration of opioids and local anesthetics is becoming increasingly popular in the management of acute postoperative pain. Recent reports have described epidural patient-controlled analgesia (PCA) with opioids (1–5) and opioid-local anesthetic combinations with continuous (basal) infusions (6–9). However, the influence of local anesthetics on epidural opioid analgesia with or without a continuous infusion has not been studied.

Most of the clinical studies comparing epidural opioids versus opioid-local anesthetic combinations have utilized the highly lipid-soluble opioids (6–9). However, the use of fentanyl and sufentanil has been questioned because of their lack of a dose-sparing effect compared with intravenous administration (10–13). When epidural hydromorphone was administered with a PCA delivery system, a marked dose-sparing effect was reported compared with intravenous PCA with hydromorphone (5).

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We designed a prospective, double-blind study to evaluate the influence of a dilute local anesthetic solution (0.08% bupivacaine) and a basal opioid infusion (hydromorphone [0.0375 mg/h]) during epidural PCA with hydromorphone. In addition to determining the opioid and local anesthetic analgesic requirements, we assessed quality of pain relief, patient satisfaction, side-effect profiles, and recovery times after elective cesarean delivery.

Methods

After approval of the study protocol by the Washington University Human Studies Committee, 170 consenting, healthy women scheduled to undergo elective cesarean delivery were randomly assigned to one of four epidural PCA treatment groups. The theoretical basis for PCA therapy and the operational aspects of the PCA device were explained at the time of the preoperative visit and were reviewed with each patient before initiating PCA therapy in the postanesthesia care unit. Patients with evidence of bacteremia or coagulopathy, as well as those who were reluctant to have an epidural catheter remain in place after their operation, were excluded.

All patients received 0.5% bupivacaine (15–25 mL) via a percutaneous lumbar epidural catheter for surgical anesthesia. Approximately 2–3 h after epidural bupivacaine administration for surgical anesthesia, a Bard Ambulatory PCA device was connected to each patient's epidural catheter. Group I (control) received a 3-mL initial dose of hydromorphone (0.075 mg/mL), with supplemental 2-mL bolus doses at a minimal lockout interval of 30 min. Group II received the same regimen as the control group, with the addition of a continuous (basal) infusion of hydromorphone (0.5 mL/h [0.0375 mg/h]). Group III received a combination of hydromorphone (0.075 mg/mL) and 0.08% bupivacaine (0.8 mg/mL) by intermittent bolus injection, as described previously for group I. Finally, group IV received the same opioid-local anesthetic combination as described for group III, with the addition of a basal infusion at 0.5 mL/h (bupivacaine [0.04 mg/h] and hydromorphone [0.0375 mg/h]). The number of delivered bolus doses and patient demands (button presses) for supplemental medication and total drug dosages were recorded for up to 48 h after the operation. The patients, nurse observers, and surgeons were all unaware of the content of the PCA solution and the presence or absence of the basal infusion.

Evaluation of postoperative respiratory function included determination of respiratory rate (which was recorded every 2 h by the ward nurses) and measurement of hemoglobin oxygen saturation with the Nellcor Oxinet telemetry system when patients were at bed rest. An alarm would sound at the nursing station when the hemoglobin oxygen saturation decreased to <85% for >1 min. Other postoperative assessments included determination of recovery times from completion of the operation to unassisted ambulation, return of bowel sounds, resumption of solid diet, and hospital discharge.

Patients assessed pain (no pain to worst pain imaginable), sedation (wide awake to nearly asleep), fatigue (well rested to completely exhausted), discomfort (comfortable to very uncomfortable), and anxiety (relaxed to anxious) levels at 8-h intervals using 100-mm linear visual analogue scales (0 = none to 100 = maximal) (14). All patients were evaluated by the primary care nurse at 2-h intervals, and all side effects (e.g., nausea, vomiting, pruritus, lower extremity paresthesia or weakness, urinary hesitancy) were noted. The Foley catheter was routinely removed on the morning after surgery. Urinary hesitancy was defined as difficulty in voiding 6 h after removal of the Foley catheter.

The incidence of side effects was considered to be the percentage of patients experiencing the side effects out of the total number of patients in the group, regardless of the number of times the side effects were noted for any individual patient. A standardized protocol was used to treat side effects if the symptoms were present on successive nursing visits or if the patient complained of persistent symptoms. The PCA therapy was discontinued when patients were able to tolerate a clear liquid diet. Postoperative PCA assessment questionnaires were completed by the patients, as well as their surgeons and primary care nurses, after completion of PCA therapy.

Opioid and local anesthetic usage, visual analogue scale scores, and recovery times were analyzed using one-way analysis of variance, with a Bartlett's post hoc test to determine differences among groups; χ^2 testing was used to analyze discrete variables. The Wilcoxon rank-sum (nonparametric) test was used to compare median values for visual analogue scale scores and number of bolus doses in the four PCA treatment groups. Changes in opioid or local anesthetic usage over time within each treatment group were evaluated with repeated measures of analysis of variance and Student's *t*-test with Bonferroni's correction. A *P* value <0.05 was considered statistically significant. Data are reported as median (and interquartile ranges) or mean ± SD (in tables) and ±SEM (in figures).

Results

From November 1988 to December 1990, 170 women were enrolled in this epidural PCA study. The four treatment groups were comparable with respect to

Table 1. Demographic and Intraoperative Data in the Four Epidural Patient-Controlled Analgesia Treatment Groups

	Group I (opioid alone; $n = 43$)	Group II (opioid infusion; $n = 46$)	Group III (opioid-local anesthetic combination; $n = 42$)	Group IV (opioid-local anesthetic infusion; $n = 39$)
Age (yr)	28 ± 6	28 ± 5	28 ± 6	28 ± 4
Height (cm)	162 ± 6	163 ± 7	160 ± 6	163 ± 7
Weight (kg)	77 ± 11	77 ± 16	77 ± 13	76 ± 19
Race (white/black)	25/18	28/18	22/20	23/16
Bupivacaine dose (mg)	130 ± 43	120 ± 53	120 ± 30	127 ± 40
Operative time (min)	67 ± 23	66 ± 26	67 ± 25	65 ± 17
Previous cesarean	28	24	22	23

PCA, patient-controlled analgesia.
Values are mean ± SD or numbers.

demographic variables (Table 1). The duration of surgery and total intraoperative epidural local anesthetic dosages were also similar in the four groups. The epidural catheter became dislodged, and PCA therapy was changed to intravenous PCA in three patients in group I (control) and in two patients in group III. Eight patients (20%) in the opioid-local anesthetic infusion group (group IV) required discontinuation of the infusion secondary to complaints of lower extremity weakness or paresthesia, or both. In addition, two patients in group I, two in group II, one in group III, and four in group IV requested discontinuation of their epidural PCA therapy because of persistent side effects. Patient data were excluded from further analysis at the time of these protocol violations.

The number of PCA demands and supplemental bolus doses was similar among all four treatment groups throughout the study period (Figure 1). The ratio of delivered doses-to-demands remained stable in all groups during the study period. Patients in the hydromorphone PCA plus basal infusion group (group II) received significantly more hydromorphone in the first 24 h of therapy (3.3 ± 1.3 mg [mean ± SD]) than the hydromorphone PCA alone group (2.1 ± 1.1 mg; $P < 0.01$). Similarly, the opioid-local anesthetic infusion group (group IV) received significantly more hydromorphone in the first 24 h (2.7 ± 1.1 mg) than the opioid-local anesthetic combination PCA group (group III) (2.0 ± 1.0 mg; $P < 0.01$). During each 4-h period after initiation of PCA therapy, more hydromorphone was administered to patients receiving a continuous opioid infusion (group II) compared with patients receiving the opioid on an intermittent PCA basis (group III) (Figure 2). Although a similar overall difference was seen between group III (opioid-local anesthetic combination without basal infusion) and group IV (opioid-local anesthetic with infusion), this difference was not as consistent. Similarly, patients in the opioid-local anesthetic infusion group (group IV) received significantly more ($P < 0.05$) bupivacaine in the first 24 h (31.5 ± 11.6 mg) than those receiving only intermittent bolus administration (23.3 ± 11.4 mg). A comparison of opioid alone without infusion versus the opioid-local anesthetic combination without infusion (i.e., group I vs. group III) revealed no significant differences in the delivered bolus dose-to-demand ratio or in the 24-h hydromorphone utilization.

Pain scores were similar at the time of initiation of PCA therapy and throughout the study in all groups (unreported data). When asked their expectations preoperatively, 33% of patients in each group anticipated severe or very severe pain after the operation. However, on the follow-up questionnaire, 95% of the patients in each group (except group III) reported experiencing only mild or moderate pain. In the opioid-local anesthetic combination group (group III), 16% of patients reported having experienced moderate to severe pain after the operation ($P < 0.05$). Overall, 94%–100% of patients reported receiving adequate postoperative pain therapy. Similarly, the nurses reported that 98% of the patients had satisfactory pain relief. Of the patients with a previous cesarean delivery ($n = 97$), 85% stated they had experienced either similar or less pain after this operation than they had previously experienced. Additionally, 80% of the patients stated they had been more active physically during the first 48 h after this cesarean delivery compared with their previous experience.

Visual analogue scale scores for sedation, discomfort, fatigue, and anxiety revealed no differences among groups during the study period (unreported data). Only 6%–12% of patients in each group reported feeling drowsy after their operation, whereas 60%–77% felt wide awake to slightly sleepy after surgery. A majority of patients in each group (56%–75%) stated they had slept well after their operation, and no differences were noted in the number of

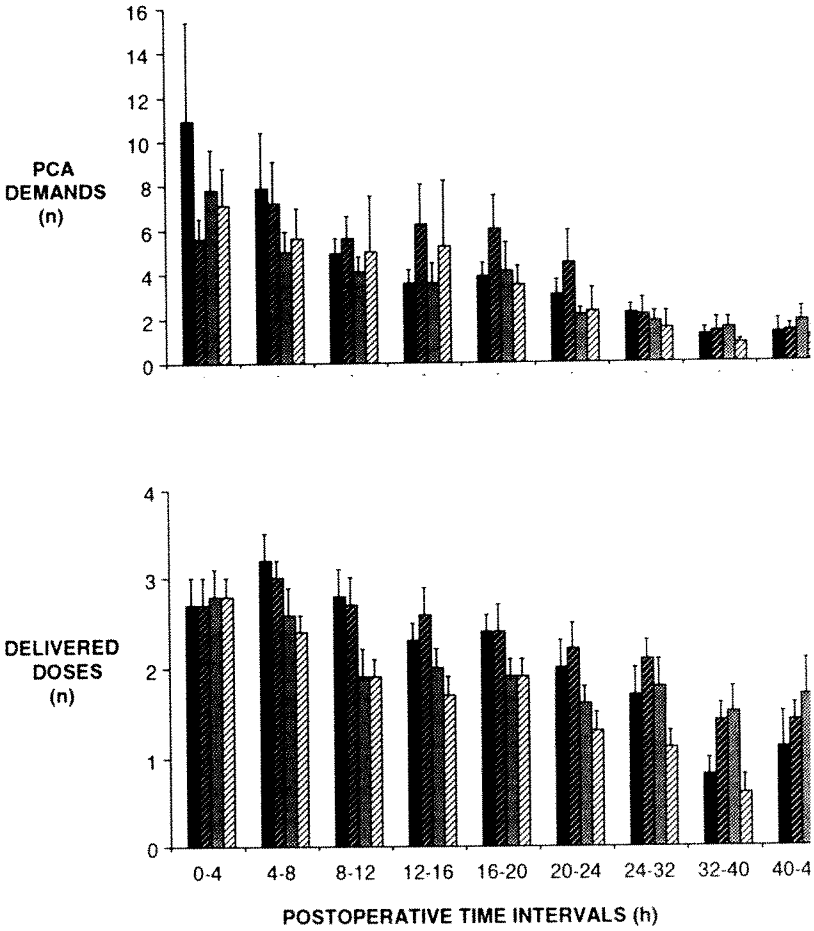

Figure 1. **(Top)** Postoperative patient-controlled analgesia (PCA) demands per 4 h. **(Bottom)** Postoperative PCA doses delivered per 4 h. *Solid bar,* opioid alone; *dark hatched bar,* opioid with basal infusion; *stippled bar,* opioid-local anesthetic; *light hatched bar,* opioid-local anesthetic with basal infusion. Values are mean ± SEM.

awakenings to self-administer pain medication among the four treatment groups. Overall, 35% of patients found it necessary to awaken so as to self-administer supplemental PCA doses. Only 18% of patients reported difficulty in sleeping due to pain. Activity in the room was the most common reason cited as the cause of difficulty in sleeping.

On the follow-up questionnaire, only 5% of patients receiving hydromorphone PCA (group I) thought that their PCA medication had contributed to postoperative nausea, whereas 25% of patients in group IV reported nausea associated with PCA administration ($P < 0.05$). In groups II and III, 16% of patients reported PCA-related nausea. This was similar to the incidence of nausea reported by the ward nurses (Table 2). Antinausea therapy was required in all groups, except in group I (opioid alone). Pruritus occurred in 55%–72% of patients, with a significantly higher incidence of intractable itching requiring antipruritic therapy in group IV (Table 2). Urinary hesitancy (Table 2) was seen in only two patients (one requiring catheter replacement) in group I. However, there was a significantly higher incidence of urinary hesitancy and catheter replacement in groups II–IV. Lower extremity paresthesia (i.e., numbness persi ing 8 h after surgery) was noted in 22% of patients group IV and resulted in discontinuation of t epidural infusion in 20% of patients in this group (because of lower extremity weakness and difficu with ambulation). No patient had a postoperat respiratory rate of <12 breaths/min. Additionally, patients had hemoglobin oxygen saturation valu <91%. All patients were able to ambulate on th own (with the exception of three in group IV hav leg weakness) within 16 ± 6 h after surgery. T times to resumption of bowel sounds (20 ± 10 solid diet (54 ± 18 h), and hospital discharge (97 19 h) were similar for all groups. According to surgeons' questionnaires, the return of bladder a bowel function was longer than expected in 25% opioid-local anesthetic infusion group patie (group IV) compared with only 8% of patients rece ing the opioid alone (group I) ($P < 0.05$). Al according to the surgeons, 33% of patients were a to ambulate earlier than expected, and 22% w ready for hospital discharge earlier than expect Ambulation and readiness for hospital discha were noted by the surgeons to be later than expec

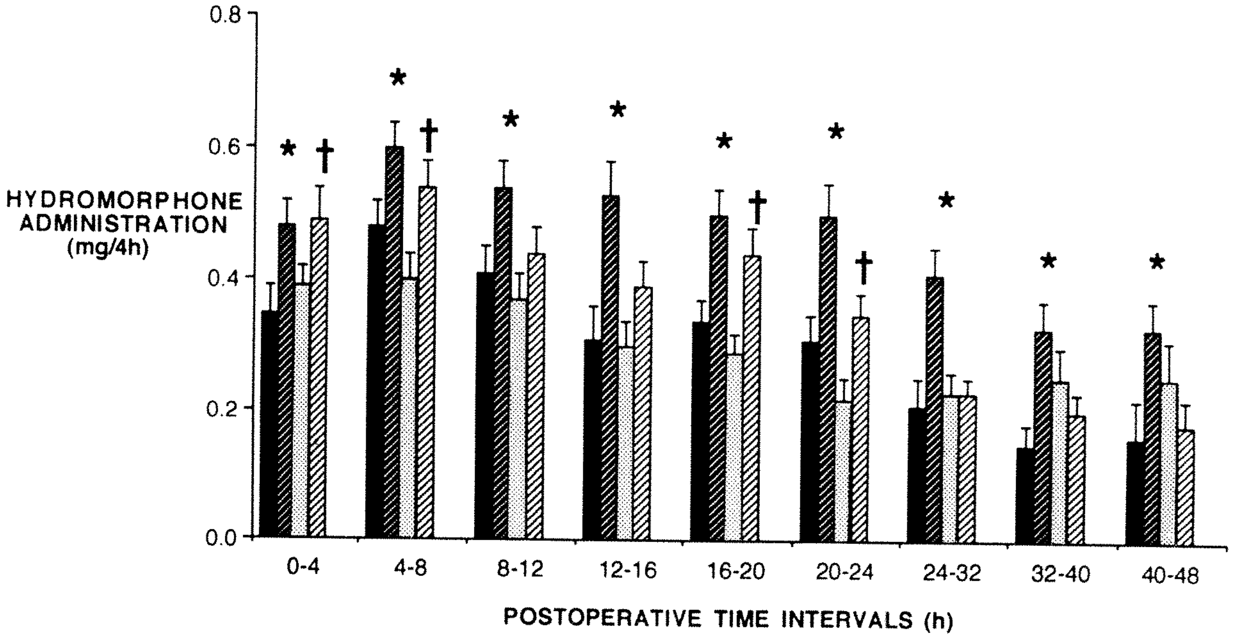

Figure 2. Postoperative hydromorphone utilization after the loading dose. *Solid bar*, opioid alone; *dark hatched bar*, opioid with basal infusion; *stippled bar*, opioid-local anesthetic; *light hatched bar*, opioid-local anesthetic with basal infusion. Values are mean ± SEM. *Significantly different ($P < 0.05$) from opioid group. †Significantly different ($P < 0.05$) from opioid-local anesthetic group.

Table 2. Percentage of Patients With Side Effects in the Four Epidural Patient-Controlled Analgesia Treatment Groups, as Reported by the Ward Nurses

Side effect[a]	Group I (opioid alone; $n = 40$)	Group II (opioid infusion; $n = 46$)	Group III (opioid-local anesthetic combination; $n = 40$)	Group IV (opioid-local anesthetic infusion; $n = 39$)
Nausea	9 (0)	20^b (9^b)	24^b (11^b)	30^b (20^b)
Vomiting	7 (2)	13 (4)	21 (11)	14 (11)
Pruritus	55 (22)	66 (24)	55 (35)	72 (42^b)
Urinary hesitancy	6 (3)	17 (17^b)	25 (23^b)	20 (20^b)
Leg numbness	0	0	0	22^b (20^b)
Leg weakness	0	0	0	8^b (8^b)

[a] Parentheses indicate the percentage of patients in each group requiring therapy for these side effects.
[b] Significantly different from the opioid group; $P < 0.05$.

in six patients, all of whom were in the opioid-local anesthetic infusion group (group IV). Overall, the surgeons reported being satisfied with the pain relief regimen in 96% of patients.

Discussion

Epidural analgesic techniques for managing postoperative pain have involved the use of both opioid analgesics and local anesthetics via either intermittent or continuous dosing methods. Unfortunately, the clinical usefulness of these studies is often limited because of problems with the study design (e.g., retrospective studies [15,16], historical controls [4], comparisons of different opioids [1], small patient populations with multiple surgical procedures [1], and comparisons of different drugs and modes of delivery [12,17–20]).

In 1988, Gambling et al. (21) reported on the role of continuous epidural infusion (vs epidural PCA) for administering bupivacaine during labor. These investigators noted that patients controlling their own drug delivery administered less medication than when a continuous infusion was used. Similarly, Marlowe et al. (2) found a decrease in the opioid requirement with epidural PCA versus epidural infusion for postoperative analgesia. Recently, Ferrante et al. (8) reported decreased bupivacaine consumption when a bupivacaine-fentanyl mixture was administered via epidural PCA compared with continuous epidural infusion of these drugs during labor. The addition of low-dose bupivacaine did not improve postoperative epidural fentanyl analgesia after knee surgery and may increase morbidity (22). Finally, Boudreault et al. (7) reported that patients utilizing epidural PCA with fentanyl to supplement a continuous infusion of epidural bupivacaine required less fentanyl than patients receiving a continuous epidural infusion of fentanyl and bupivacaine after laparotomy procedures.

Our data suggest that satisfactory postoperative pain relief after cesarean delivery can be obtained with less opioid medication when patients self-administer bolus doses of hydromorphone via epidural PCA, either alone or in combination with bupivacaine, compared to PCA with a continuous basal infusion. However, we were unable to demonstrate any advantage in combining local anesthetic with hydromorphone compared with hydromorphone alone in this postsurgical population. In addition, the administration of a hydromorphone-bupivacaine mixture with a basal infusion resulted in more nausea and difficulty with voiding and ambulation than the other epidural analgesic techniques. The use of a basal infusion, with or without local anesthetic, led to higher opioid usage without decreasing the pain scores or the number of patient demands for analgesic medication. These data confirm our previous findings involving intravenous PCA with or without a basal infusion (23). Analogous to the findings in our recent study in which a nighttime intravenous infusion was combined with PCA (24), we were unable to demonstrate any improvement in the patients' ability to sleep when an epidural infusion was utilized. Moreover, none of the patients receiving epidural PCA alone (groups I and III) required the addition of a basal infusion to optimize their postoperative pain management.

In this study, all women were able to achieve satisfactory pain relief without excessive sedation or evidence of respiratory depression. With the exception of 17 patients (12 in group IV), all patients successfully completed the study protocol without side effects necessitating changes in their initial PCA prescription. The use of a more dilute solution of bupivacaine (e.g., 0.015%) (9) might have decreased the number of patients in group IV requiring discontinuation of their PCA therapy. However, the use of more dilute bupivacaine solutions may not produce the desired local anesthetic effect. In preliminary dose-ranging studies, we found that 0.125% bupivacaine (6.25 mg/h) interfered with early ambulation in all patients and that 0.02% bupivacaine (1 mg/h) had no clinically apparent effect.

Although there was no evidence of intravascular, subdural, or subarachnoid catheter migration, the catheter became dislodged in 5 of the first 27 patients enrolled in the study. This problem was avoided in the remaining patients by using a more secure method of taping the catheter in place (5). Nevertheless, catheter migration or dislodgment, or both, is a potential problem in using epidural catheter techniques for postoperative analgesia (25–28). In addition, subarachnoid infection has been reported in patients receiving epidural analgesia after cesarean section (29). Finally, a programming error when utilizing the basal infusion mode may have greater consequences than with the conventional intermittent dosing technique (30).

One limitation of this double-blind study is the inability to extrapolate our results to other postsurgical populations. Future studies should include both men and women undergoing upper abdominal, thoracic, and major joint replacement procedures to further define the role of epidural PCA. A second criticism relates to the apparently arbitrarily chosen bolus doses (and drug concentrations), lockout intervals, and basal infusion rates. However, these PCA variables were determined to provide adequate analgesia in preliminary dose-ranging studies. More importantly, because patients were able to self-administer additional medication using the PCA device, these factors should not have significantly affected our findings.

In conclusion, epidural PCA with hydromorphone is a safe and effective method of providing pain relief after elective cesarean delivery. The addition of 0.08% bupivacaine or a basal hydromorphone infusion, or both, increased side effects without improving the patients' pain relief.

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Nalbuphine Is Better Than Naloxone for Treatment of Side Effects After Epidural Morphine

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This study compared naloxone and nalbuphine when administered for treatment of side effects after epidural morphine, 5 mg, given for postcesarean analgesia. Patients requesting treatment for pruritus or nausea randomly received, in a double-blind fashion, up to three intravenous doses of either naloxone 0.2 mg (group 1; $n = 20$) or nalbuphine 5 mg (group 2; $n = 20$). The incidence of vomiting, the severity of nausea and pruritus, and the degree of sedation and pain were assessed before and 30 min after each dose. The first dose of nalbuphine decreased the incidence of vomiting ($P < 0.005$) and the severity of nausea and pruritus ($P < 0.01$), whereas naloxone caused no significant changes. Sedation scores increased after nalbuphine ($P < 0.05$) and remained unchanged after naloxone, whereas pain scores increased after naloxone ($P < 0.01$) and were unchanged after nalbuphine. Eighteen patients in group 1 and 12 in group 2 received a second dose, and 8 and 4 patients, respectively, a third dose. Other than decreased pruritus after the second dose with both drugs, no further changes occurred. We conclude that nalbuphine is superior to naloxone for the treatment of side effects after epidural morphine. However, persistent symptoms may require supplemental therapy, as repeated doses proved less effective than the initial dose.

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Epidural morphine provides excellent postoperative analgesia but is associated with a high incidence of troublesome side effects such as pruritus, nausea, and vomiting (1–7). In a previous study of women receiving epidural morphine for postcesarean section pain in our institution, 85% complained of pruritus and 59% of nausea (1). Prophylactic administration of naloxone or nalbuphine has been recommended to prevent these side effects (8,9). However, because only about 50% of patients require treatment (1), many would receive drug therapy unnecessarily. In addition to possible side effects from the drugs themselves, routine prophylactic injections of naloxone or nalbuphine to all women receiving epidural morphine after cesarean delivery would result in increased costs and added nursing workload. The current study was designed to compare the efficacy and adverse effects of nalbuphine and naloxone administered therapeutically to patients requesting treatment for side effects caused by epidural morphine given during cesarean section.

Methods

After approval of the study by the Human Subjects Committee, written informed consent was obtained from healthy women undergoing nonemergency cesarean section with epidural anesthesia. The majority of patients were having scheduled cesarean sections; the remainder were in labor, some with an epidural catheter already in place. Patients were excluded from the study if they had received opioids other than epidural fentanyl, 50–100 μg, either alone or in combination with dilute bupivacaine for labor analgesia. Antiemetics were not administered routinely, although metoclopramide, 10 mg IV, occasionally was given intraoperatively for treatment of nausea or vomiting. Patients could receive intravenous midazolam, 0.5–1 mg, or fentanyl 50–100 μg, intravenously or epidurally, for anxiety or discomfort during operation.

Immediately after delivery, all potential subjects received preservative-free epidural morphine, 5 mg in 10 mL, via the epidural catheter. Approximately 45% of patients subsequently requested treatment for pruritus, nausea, or vomiting. These individuals were entered into the study and randomly received in a double-blind manner either naloxone, 0.2 mg IV (group 1; $n = 20$) or nalbuphine, 5 mg IV (group 2;

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Table 1. Patient Characteristics and Times to Study Drug Administration

	Group 1 (naloxone) (n = 20)	Group 2 (nalbuphine) (n = 20)
Age (yr)	31 ± 1	33 ± 1
Weight (kg)	76 ± 2	79 ± 3
Height (cm)	160 ± 2	165 ± 1
Time to dose 1 (min)[a]	238 ± 18	235 ± 20
Time to dose 2 (min)[a]	307 ± 22	312 ± 15
Time to dose 3 (min)[a]	326 ± 39	385 ± 40

Values are mean ± SEM. There were no significant differences.
[a] Time from administration of epidural morphine.

Table 2. Symptoms for Which Treatment Was Requested

	Group 1 (naloxone) (n = 20)	Group 2 (nalbuphine) (n = 20)
Nausea and/or vomiting	4	5
Pruritus	12	4[a]
Both (nausea & pruritus)	4	11[a]

Values represent numbers of patients.
[a] $P < 0.05$ vs group 1.

Table 3. Nausea Severity Scores (0–3) Before and After the First Dose of Study Drug

	Group 1 (naloxone) (n = 10)	Group 2 (nalbuphine) (n = 16)	P between groups (Mann–Whitney test)
Pre-dose 1 score	2	2	NS
Post-dose 1 score	1.5	0[a]	0.015
Change in score	−0.5	−1	0.015

NS, not significant.
Values are median scores among patients receiving treatment for nausea.
[a] $P < 0.001$ vs predose score (Wilcoxon signed rank test).

Table 4. Pruritus Severity Scores (0–3) Before and After the First Dose of Study Drug

	Group 1 (naloxone) (n = 16)	Group 2 (nalbuphine) (n = 16)	P between groups (Mann–Whitney test)
Pre-dose 1 score	2	1.5	NS
Post-dose 1 score	1	1[a]	0.04
Change in score	−0.5	−1	NS

NS, not significant.
Values are median scores among patients receiving treatment for pruritus.
[a] $P < 0.005$ vs predose score (Wilcoxon signed rank test).

n = 20). Study drugs were prepared by an anesthesiologist not involved in the study. If symptoms persisted, up to two additional doses of the same drug could be given at no less than 30-min intervals. The patient was asked to state which symptom was her primary reason for requesting treatment. Before, and 30 min after injection of each dose of study drug, the following assessments were made: presence and severity of nausea or pruritus (rated by the patient as none, mild, moderate, or severe and assigned scores of 0–3); whether vomiting had occurred; and the degrees of sedation and pain. The latter were quantified by the patient using a verbal pain scale (VPS) where 0 = no pain and 10 = worst pain imaginable, and a verbal sedation scale (VSS) where 0 = completely awake and 10 = almost asleep. These scales are comparable to visual numerical rating (10) or visual analogue pain and sedation scales (11) previously described. The study was terminated after three doses of the study drug had been given, or earlier at the patient's request. Continuing side effects were treated with further doses of naloxone or nalbuphine, or with metoclopramide for nausea and diphenhydramine for pruritus. Pain during the study period was treated with small (12.5–25 mg) doses of intravenous meperidine. Overall pain relief and efficacy of treatment for side effects were evaluated by the patient on the day after delivery as poor, fair, good, or excellent.

Data were analyzed using Student's t-test for continuous data, Mann-Whitney and Wilcoxon signed rank test for nonparametric data (pruritus and nausea scores, VPS, and VSS), and χ^2 or Fisher's exact test for categorical data. $P < 0.05$ was considered significant.

Results

The groups were similar with respect to age, weight, height (Table 1), and the incidence of elective cesarean sections (group 1: 51%, group 2: 49%). One patient in group 1 and three in group 2 had received epidural fentanyl during labor. With the exception of one patient in each group who received 0.5% bupivacaine, 2% lidocaine with 1:200,000 epinephrine was used to provide surgical anesthesia. Two patients in each group experienced intraoperative nausea and vomiting for which three of the four received metoclopramide.

The times from epidural morphine administration to the first dose of study drug are shown in Table 1, and the symptoms for which patients requested treatment in Table 2. More patients in group 2 than in group 1 complained of both nausea and pruritus (Table 2; $P < 0.05$) and more had vomited (65% vs 25%, $P < 0.05$). Before treatment, the severity of nausea and pruritus was similar in both groups (Tables 3 and 4). The first dose of nalbuphine decreased the incidence of vomiting ($P < 0.005$) and the severity of both nausea and pruritus ($P < 0.005$;

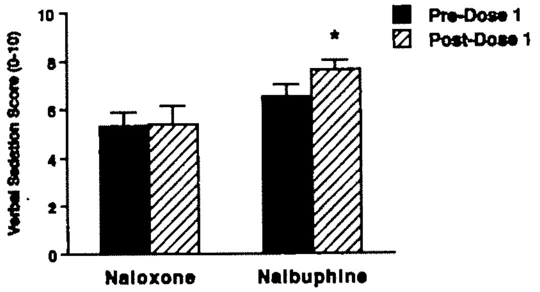

Figure 1. Verbal sedation scores (mean ± SEM) before, and 30 min after, administration of the first dose of naloxone or nalbuphine. *$P < 0.05$ versus predose score (Wilcoxon signed rank test).

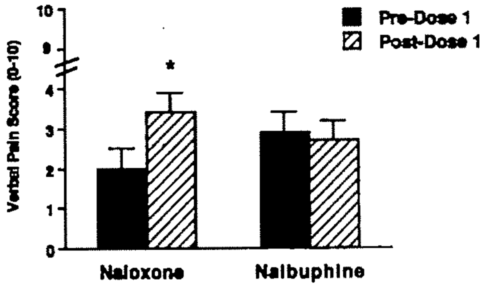

Figure 2. Verbal pain scores (mean ± SEM) before, and 30 min after, administration of the first dose of naloxone or nalbuphine. *$P < 0.05$ versus predose score (Wilcoxon signed rank test).

Tables 3 and 4), while naloxone caused no change in vomiting or the severity of nausea (Table 3), and a decrease in the severity of pruritus that just failed to reach statistical significance ($P = 0.06$; Table 4). Nalbuphine completely abolished nausea in 69% of patients with this symptom, compared with only 20% for naloxone ($P < 0.05$). Pruritus was abolished in 25% of patients after nalbuphine and none after naloxone ($P = 0.1$). Sedation scores increased after the first dose of nalbuphine ($P < 0.05$) and remained unchanged after naloxone (Figure 1), whereas pain scores increased after naloxone ($P < 0.01$) and remained unchanged after nalbuphine (Figure 2). (Mean scores are shown in these figures as the authors believe they illustrate central tendency in the groups better than median values; statistical comparisons were performed with appropriate nonparametric tests.)

Eighteen patients in group 1 and 12 in group 2 received a second dose, and 8 and 4, respectively, a third dose of study drug (NS). As with the first dose, the times from morphine administration to subsequent doses were similar in both groups (Table 1). Dose 2 of nalbuphine abolished nausea and pruritus in 43% and 45% of patients, respectively, compared with 0% and 34% for these symptoms with naloxone (NS between groups). The severity of pruritus decreased significantly after the second dose of both drugs ($P < 0.05$ vs predose scores). However, there were no statistically significant changes in the severity of nausea, although scores tended to improve after nalbuphine ($P = 0.1$). The third dose of study drug failed to improve symptoms in either group. Sedation and pain scores did not change significantly after the second or third dose of either drug.

Neither cardiovascular changes nor respiratory depression (respiratory rate ≤10 breaths/min) were observed during the study. Overall pain relief scores were similar in both groups, with 89% of patients in group 1 and 85% in group 2 rating their pain relief as good or excellent. Requirements for supplemental analgesia were similar in both groups, with seven patients in each group receiving intravenous meperidine during the study period (average cumulative doses of 22 ± 9 mg in group 1, and 27 ± 7 mg in group 2; NS). Three patients in group 1 and two in group 2 received meperidine in the period between the first and second doses of study drug (NS). Fifty percent of patients in group 2 rated their relief of side effects as good or excellent, compared with only 26% in group 1; however, this difference was not statistically significant.

Discussion

Side effects with intraspinal opioids, particularly hydrophilic agents such as morphine, occur with great frequency in the obstetric population (1–7). Among patients receiving epidural morphine 2–5 mg after cesarean section, 53%–93% complain of pruritus, and 34%–59% of nausea and vomiting (1–7). Although this therapy produces better pain relief after cesarean delivery than do systemic opioids (1,4), the associated side effects can prove incapacitating. Patients at our institution cited nausea as the most common reason for delay in walking after epidural morphine, whereas pain was the most common reason in patients receiving systemic opioids (1).

Various approaches have been explored to prevent or treat these side effects. Phenothiazines have been used as antipruritics, and metoclopramide, droperidol, and transdermal scopolamine as antiemetics (12,13). Because these drugs often treat only one symptom, multiple drug therapy may be necessary. Another drawback of these agents is their potential for causing sedation, thereby increasing the risk for respiratory depression (6,12). To avoid these problems, specific opioid antagonists have been used with the goal of counteracting all the side effects of intraspinal opiates with one drug. Naloxone, a predominantly μ-receptor antagonist, and nalbuphine, a drug with mixed μ-antagonist and κ-agonist effect, both have been used for this purpose. In the current study we found that nalbuphine was clearly superior to naloxone for the treatment of nausea and pruritus. In most previous studies these drugs have been administered prophylactically rather than therapeutically, with inconsistent results regarding their efficacy and their effect on analgesia.

In surgical patients, Rawal et al. (14) observed reversal of epidural morphine-induced respiratory depression by naloxone infused at 5 or 10 $\mu g \cdot kg^{-1} \cdot h^{-1}$. Other side effects were minimally affected and, as in another study in which 0.4–4 $\mu g \cdot kg^{-1} \cdot h^{-1}$ was infused (15), the higher naloxone dose adversely affected analgesia. Korbon et al. (8) gave intermittent intramuscular naloxone injections to cesarean section patients who had received epidural morphine, demonstrating reversal of respiratory depression, insignificant decreases in pruritus and nausea, and no effect on analgesia. In a similar population, Daly et al. (16) infused naloxone at 0, 0.05, 0.1, and 0.2 mg/h, reporting no differences in analgesia but significantly decreased pruritus scores with the highest dose; a tendency for dose-related decreases in pruritus and nausea was claimed. In contrast, Ramanathan et al. (17) found no differences in side effects but increased pain scores when naloxone 0.1 mg/h was infused after cesarean section at which epidural morphine was given. In a similar study, Thind et al. (18) found the benefits of naloxone infusion limited to a decreased severity of pruritus. Although some of these investigators advocate use of prophylactic naloxone to prevent nonrespiratory side effects, their recommendations often are based on findings that failed to reach statistical significance (8,16).

Prophylactic nalbuphine administration also has proved controversial. In surgical patients, nalbuphine boluses of 0.3 mg/kg (9), or 200 $\mu g/kg$ followed by an infusion of 50 $\mu g \cdot kg^{-1} \cdot h^{-1}$ (19), reversed respiratory depression after epidural morphine without affecting analgesia. Decreased pruritus was noted after 0.1 mg/kg of the bolus had been injected (9). In contrast, Morgan et al. (20) found that three prophylactic doses of intravenous nalbuphine given at 0, 6, and 12 h after epidural morphine administered at cesarean section failed to prevent decreases in respiratory rate or oxyhemoglobin saturation and had no effect on pruritus. However, the authors comment that because respiratory monitoring was intermittent and because patients often received intraoperative and postoperative sedatives or phenothiazines, firm conclusions could not be drawn regarding the effect of nalbuphine on respiration. Although our finding that nalbuphine decreased pruritus appears to contradict those of Morgan et al. (20), this may relate to differences in study design and methodology. Because we administered nalbuphine only to patients requesting treatment for side effects, whereas Morgan et al. (20) gave the drug prophylactically to all patients, our study might be more sensitive in demonstrating an effect. Also, we measured decreases in the severity of pruritus 30 min after injection of nalbuphine in symptomatic patients, whereas they recorded the average maximum pruritus score noted during the entire 18-h study period. Our data probably reflect the benefit associated with peak drug concentrations, whereas theirs may reflect the severity of symptoms occurring when nalbuphine concentrations were at their lowest.

We believe that prophylactic administration of naloxone or nalbuphine to prevent side effects of epidural morphine is not justified, and that treatment should be administered only to patients who develop symptoms. As we were unaware of other investigations comparing therapeutic administration of these drugs, we designed this study to determine their relative benefits and side effects. Our findings that nalbuphine more effectively relieved side effects while preserving analgesia supports its use in preference to naloxone. Although reversal of analgesia with naloxone might not have occurred had we given smaller doses, we selected relatively large boluses of each drug to maximize both beneficial and adverse effects. The 0.2-mg naloxone and 5-mg nalbuphine doses we used are in the ratio of 1:25, which approximates the 1:34 antagonist potency ratio for these drugs quoted by Schmidt et al. (21) and the 1:31 ratio for reversal of fentanyl-induced respiratory depression reported by Bailey et al. (22).

Nalbuphine potentially might improve analgesia via its agonist effect at the κ-receptor, or diminish it by antagonism at the μ-receptor. Indeed, studies in rats suggest a complex analgesic interaction between intraspinal morphine and systemic nalbuphine, depending on the relative doses of each, the time after nalbuphine administration, and the nature of the nociceptive stimulus (23). Reversal of epidural morphine analgesia by nalbuphine has not been described in humans (9,19), although decreased analgesia has occurred after nalbuphine administration to counteract respiratory depression after high (22,24,25) but not lower (26) doses of intravenous fentanyl. The degree of reversal of analgesia noted in these studies appears to be less than that found with naloxone, particularly when small doses of nalbuphine were used (22,24). One case report has described improved analgesia and reversal of side effects by nalbuphine in a patient who had received epidural morphine after cesarean section (27).

In the current study, we found no change in analgesia after nalbuphine, whereas pain scores increased significantly after naloxone. Although this did not result in different meperidine utilization in the two groups, we believe that increased pain scores are more sensitive indicators of patient discomfort than is systemic opioid dosage; pain scores were carefully evaluated by the investigators, whereas meperidine was administered at the discretion of the postpartum nurse. Any supplemental analgesic given to treat pain conceivably could have affected some of the outcome variables measured (e.g., nausea or pruritus). We selected meperidine because it lacks opioid antagonist effect and, in small boluses, causes minimal nausea or pruritus. As both groups received similar doses of meperidine, it is unlikely to have significantly modified our results.

In common with other investigators (9,19,20), we found increased sedation after the first nalbuphine injection, which did not worsen with subsequent doses (19). In spite of this, overt respiratory depression did not occur in any patient. Most studies in which arterial blood gases have been measured indicate that nalbuphine reverses respiratory depression from epidural morphine, despite causing increased sedation (9,19). Although, Morgan et al. (20) described several cases of respiratory depression in patients who had received nalbuphine, problems also occurred in the control group, and sedation by other depressant drugs probably was contributory. Close respiratory monitoring is advisable if drugs such as phenothiazines or systemic opioids are administered to patients who are sedated following nalbuphine given after intraspinal opioids. Although we found nalbuphine more satisfactory than naloxone for relieving pruritus and nausea, the duration of effect was limited. Some patients experienced persistent symptoms for which repeated treatment with the study drug proved less effective. Because fewer patients received second and third doses, analysis of these data is less reliable. Lack of a prolonged effect is not surprising, however, as the duration of both drugs is shorter than the usual duration of side effects. In a study comparing naloxone and nalbuphine given prophylactically as a basal infusion with additional self-administered doses, Kendrick et al. (28) also found nalbuphine more effective in preventing pruritus after epidural morphine. However, differences were apparent only during the first 8 h, with pruritus generally declining thereafter in both groups. If treatment of symptomatic patients is initiated with a nalbuphine bolus, supplemental therapy may be necessary for continuing symptoms. Whether a nalbuphine infusion is preferable to using conventional antipruritics or antiemetics in this circumstance has not been investigated.

In conclusion, we found that nalbuphine was better than naloxone for the initial treatment of pruritus and nausea caused by epidural morphine given during cesarean section. In addition to proving ineffective, naloxone partially reversed analgesia. Nalbuphine caused increased sedation but this had no obvious detrimental effects.

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Adverse Effects of Epidural 0.03% Bupivacaine During Analgesia After Cesarean Section

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To develop a regimen that would provide good analgesia after cesarean section with minimal side effects in the setting of prolonged (>24 h) epidural infusion, buprenorphine or fentanyl was combined with 0.03% bupivacaine in a double-blind study of 23 parturients. Patients were randomly assigned to two groups: group I (n = 12), patient-controlled analgesia by epidural infusion of buprenorphine (3 μg/mL) with 0.03% bupivacaine; group II (n = 11), patient-controlled analgesia by epidural infusion of fentanyl (2 μg/mL) with 0.03% bupivacaine. Plasma for determination of opioid concentrations was obtained at intermittent intervals. Pain relief was similar and satisfactory in both groups. The median overall satisfaction score was higher (10.0 vs 7.5; $P < 0.03$) for group II. Pruritus was mild in most patients. Nausea and vomiting, which were most disturbing to t patients, were seen only with buprenorphine. I patient had a respiratory rate of <12 breaths/mi Mean plasma opioid concentrations did not exce 1 ng/mL during the study. However, four patie (33%) in group I and six patients (55%) in group experienced sensory loss in the lower extremiti which made ambulation difficult. One patient in ea group developed extensive pressure blisters on bo heels. These complications led us to terminate t study. We conclude that 0.03% bupivacaine used combination with an opioid in prolonged epidu infusions produces a high incidence of sensory loss the lower extremities and is unsuitable for situatio in which early ambulation is desired.

(Anesth Analg 1992;75:753-

Epidural use of local anesthetics for postoperative analgesia has been associated with adverse effects, such as hypotension, lower extremity sensory loss, pressure sores, and difficulty with ambulation (1–8). Epidural administration of fentanyl to provide postoperative analgesia is popular because of low incidence of side effects, such as nausea, vomiting, respiratory depression, and urinary retention (9). Buprenorphine, an opioid agonist/antagonist with a very high lipid solubility and affinity for the opioid receptor, has been reported to provide satisfactory postoperative analgesia with few serious side effects when administered epidurally (10,11) and might be superior to fentanyl for this purpose. Opioids have been administered epidurally in combination with local anesthetics to reduce the effective concentration of either drug and thus minimize side effect 14).

The objective of this investigation was to de regimen associated with minimal opioid- anesthetic-induced side effects in the settir prolonged (>24 h) epidural infusion after c section. Fentanyl combined with 0.03% bupi and buprenorphine combined with 0.03% acaine, at doses of these opioids found in our to be equipotent, were compared with re quality of analgesia, ease of ambulation, ar dence of side effects. In addition, we dete plasma concentrations of both opioids dur infusion to determine whether either drug a lates in plasma.

Methods

The study was approved by the Institutional Board of the Albert Einstein College of Medici written, informed consent was obtained fro patient. Twenty-three ASA physical status I–I rients at term, scheduled for elective cesarean under epidural anesthesia, were included. I

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known to use sedatives or analgesics were excluded. After the subjects received 30 mL of 0.3 M sodium citrate and an infusion of 1.5–2 L of lactated Ringer's solution, continuous lumbar epidural anesthesia to achieve a T4-6 sensory level was established by injecting 3 mL of 3% 2-chloroprocaine with 5 μg/mL of epinephrine followed by 0.5% bupivacaine with epinephrine (2 μg/mL) via a catheter placed at the L3-4 interspace. The epidural catheter was directed cephalad 3 cm into the epidural space. No opiates were administered before or during the surgical procedure.

On arrival in the postanesthesia care unit, patients were randomly allocated to one of two groups: group I ($n = 12$) received continuous epidural patient-controlled analgesia (PCA) infusion of buprenorphine (3 μg/mL) with 0.03% bupivacaine diluted in saline. Group II ($n = 11$) received continuous epidural PCA infusion of fentanyl (2 μg/mL) with 0.03% bupivacaine diluted in saline.

The solutions used were placed in coded bottles, and neither the investigator nor the patient was aware of their contents. The epidural catheter was connected to a portable Pancreatec 5500-mini infuser (Pancreatec Inc., San Diego, Calif.), and each patient received an initial infusion at the rate of 10 mL/h, with self-administered 10-mL bolus doses every 2 h as desired.

Every 4 h or sooner, if requested, an investigator evaluated the patient for side effects and quality of analgesia. When required, he also altered the infusion rate and administered additional 10-mL bolus doses to achieve adequate analgesia. No patient received systemic opioids or sedatives during this treatment. The decision that the infusion was no longer necessary was made by the patient, but in no case was the duration of the infusion <24 h. Pain intensity was evaluated by using a 10-point visual analogue scale in which progressive changes in facial expression indicated degree of pain (0 = no pain; 10 = most severe pain). Overall satisfaction with the infusion was assessed by using a 10-point scale (0 = no satisfaction; 10 = best satisfaction). The patients were rated for side effects using a three-point scale (1 = mild; 2 = moderate; 3 = severe). Vital signs were monitored every 1–2 h by a nurse. Assisted by a nurse, patients started to ambulate 12–24 h after initiation of the study. On each occasion, heart rate and arterial blood pressure were measured at the start of ambulation. All of the patients had a urethral catheter inserted before and removed 12–24 h after surgery.

Plasma levels of fentanyl and buprenorphine were determined at 0, 1, 4, 8, 12, 36, and 48 h from the onset of epidural PCA infusion. Venous blood samples were obtained from an antecubital vein and, after centrifugation, plasma was separated and stored at −20°C until analysis. Plasma concentrations of fentanyl were determined using a radioimmunoassay kit (Research Diagnostics, Flanders, N.J.) (15). Plasma concentrations of buprenorphine were determined by Hazelton Laboratories Corp. (Vienna, Va.) using radioimmunoassay (16). The fentanyl assay has a limit of detection of 0.1 ng/mL and a coefficient of variation of 6.0%; the corresponding values for the buprenorphine assay are 0.1 ng/mL and 7.6%, respectively. Data were analyzed using repeated measures analysis of variance, Fisher's exact test, and Wilcoxon rank sum tests where appropriate; $P < 0.05$ was considered significant.

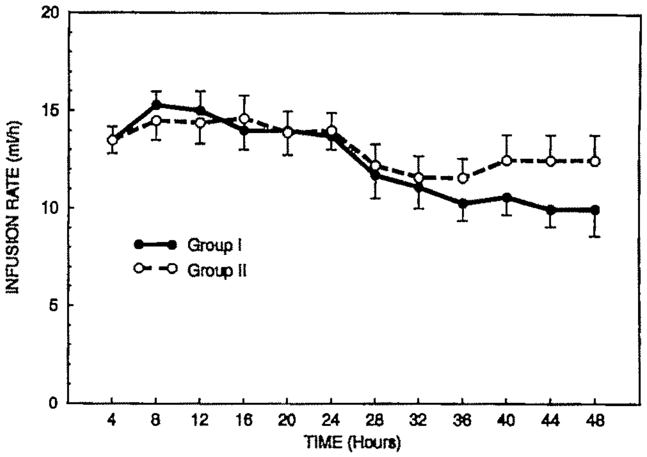

Figure 1. Patient-controlled analgesia epidural infusion rates. Values are mean ± SE. Data were analyzed by repeated measures analysis of variance. There were no differences between groups I and II.

Results

There were no differences between the groups with respect to age, height, weight, or parity. The durations of infusions for groups I and II were 34.2 ± 2.5 h (mean ± SE) and 39.0 ± 3.2 h, respectively. There were no differences in infusion rates (Figure 1) and the volume received as bolus doses between the two groups throughout the study (analysis of variance). Pain relief was satisfactory and similar (Table 1). The median overall satisfaction score was 7.5 for group I and 10 for group II ($P < 0.03$, Wilcoxon rank sums). The total incidence of pruritus for patients in group I (50%) did not differ significantly from that in group II (73%) (Fisher's exact test). Pruritus severe enough to require treatment occurred in only one patient in group I. Sedation was common, 58% in group I and 55% in group II. Sedation was never more than mild and occasioned no patient complaints. Nausea and vomiting were seen only in patients treated with buprenorphine, 33% and 25%, respectively. No pa-

Table 1. Pain Scores[a]

Time of study (h)	Group I		Group II	
	Mean (SE)	*n*	Mean (SE)	*n*
1	2.8 (0.9)	12	1.3 (0.7)	11
4	2.9 (0.8)	12	2.5 (0.7)	11
8	2.3 (0.4)	12	2.0 (1.0)	11
24	2.4 (0.6)	12	1.8 (0.9)	11
36	2.1 (0.4)	7	0.8 (0.4)	9
48	2.3 (0.5)	2	1.2 (0.4)	4

Data were analyzed by repeated measures analysis of variance. There were no significant differences between the groups.

[a] Pain scale: 0 = no pain; 10 = most severe pain.

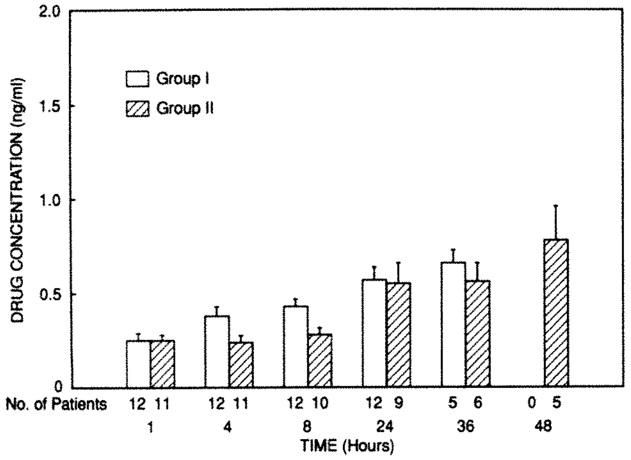

Figure 2. Plasma concentrations of buprenorphine (group I) and fentanyl (group II) are shown as mean ± SE at intervals throughout the study. No samples were obtained from group I patients at the 48-h time.

tient had a respiratory rate of <12 breaths/min or developed urinary retention. Four patients in group I (33%) and six in group II (55%) experienced sensory loss in the lower extremities, which made ambulation difficult. One patient in each group developed pressure blisters on the heels. The total bupivacaine dose over time for patients who developed numbness compared with those who did not was 4.2 ± 1.0 mg/h (mean ± SD) versus 4.2 ± 0.4 mg/h, respectively, in group I and 4.0 ± 0.9 mg/h versus 4.1 ± 0.9 mg/h, respectively, in group II. These differences were not significant. Mean plasma opioid concentrations remained <1 ng/mL throughout the infusion (Figure 2).

Discussion

The goal of this study, to develop a regimen that would provide satisfactory analgesia with minimal side effects and would not interfere with ambulation during a prolonged epidural PCA infusion after cesarean section, was only partially attained. Both infusion regimens were associated with low pain scores and high overall satisfaction scores and were without serious side effects. However, the occurrence of sensory loss in the lower extremities in 43% of our patients made ambulation difficult and in some individuals led to the development of heel blisters. This caused us to terminate the study midway.

Motor block and sensory loss in the lower extremities as well as heel sores have been reported in patients receiving postoperative analgesia with epidural infusions of 0.1% bupivacaine (3–5) or greater (6–8) in combination with opioids. Fischer et al. (4) reported a 61% incidence of numbness in the buttocks and a 74% incidence of leg weakness during epidural infusion of an opioid (fentanyl or morphine) with 0.1% bupivacaine for 24 h after cesarean section. In their report, 39% of the patients could not ambulate. In a previously published study (17), we avoided this problem by using 0.015% bupivacaine, a very much lower concentration. Although patient satisfaction was very high in general, the opioid-induced side effects of nausea, vomiting, and pruritus were bothersome to some. It was hoped that in this study, increasing the concentration of epidural bupivacaine to 0.03% would reduce the use of opioid and, consequently, the frequency of side effects. Indeed, the total dose of fentanyl used in this study was 30% lower. However, prolonged epidural infusion of 0.03% bupivacaine, in combination with fentanyl or buprenorphine, resulted in a frequent occurrence of sensory loss in the lower extremities without a reduction in the incidence of nausea, vomiting, and pruritus. We conclude that epidural 0.03% bupivacaine is unsuitable for prolonged postoperative analgesia because its use interferes with early ambulation.

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Preoxygenation of Pregnant and Nonpregnant Women in the Head-Up Versus Supine Position

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The influence of preoxygenation in the supine (n = 10) versus the 45° head-up (n = 10) position on the duration of apnea leading to a decrease in arterial oxygen saturation to 95%, as monitored by pulse oximetry, was investigated in 20 women undergoing elective cesarean section at term of pregnancy. The results were compared with those obtained in a control group of 20 nonpregnant women. In the supine position, the average time to desaturation to 95% was significantly shorter in the pregnant group (173 ± 4.8 s [mean ± SD]) than in the control group of nonpregnant women (243 ± 7.4 s). Using the head-up position resulted in an increase in the desaturation time in the nonpregnant group (331 ± 7.2 s) but had no significant effect in the pregnant group (156 ± 2.8 s). We conclude that pregnant women desaturate their arterial blood of oxygen more rapidly than do nonpregnant women. Furthermore, the head-up position extends the duration of apnea that can take place before desaturation occurs in nonpregnant patients.

(Anesth Analg 1992;75:757–9)

Preoxygenation is mandatory before "rapid-sequence" induction of general anesthesia in pregnant women (1,2), because they are at high risk for regurgitation and aspiration of gastric contents. Preoxygenation results in denitrogenation of the lungs (3), leading to an increase in oxygen reserve and delayed onset of hypoxia during apnea.

During pregnancy, the functional residual capacity of the lungs (FRC) is decreased, with further reduction occurring in the supine position (4). This decrease of FRC is compounded by the increase in oxygen consumption (5). As a result, the reduction in arterial oxygen tension during apnea is significantly greater in pregnant than in nonpregnant women (1).

Raising the awake pregnant woman to the upright position increases FRC (3) and Pa_{O_2} and reduces Pa_{CO_2} while breathing room air (6). Thus, it is speculated that arterial desaturation during apnea may be delayed in the pregnant patient if induction of anesthesia is accomplished in the head-up position (7,8).

We therefore investigated, in parturients about to undergo cesarean section, the effects of the supine versus the 45° head-up position on the duration of apnea, which would lead to a decrease in arterial oxygen saturation to 95%. The results were compared with those obtained in a control group of nonpregnant women.

Methods

The investigation was approved by the Institutional Research Committee, and informed consent was obtained from all patients. Twenty term-pregnant patients about to undergo elective cesarean section under general anesthesia were enrolled in the investigation. Patients with a history of hypertension, preeclampsia, anemia, diabetes, chronic smoking, or other conditions that might influence respiratory function or oxygen delivery were excluded. Patients with signs of fetal distress or abnormality were also excluded. Preoxygenation, rapid-sequence induction of anesthesia, and tracheal intubation were accomplished in the supine position in 10 patients and in the 45° head-up position in the remaining 10.

In all cases, arterial oxygen saturation was monitored continuously, with a pulse oximeter applied to the thumb, beginning while patients were breathing room air. They were then given oxygen (8 L/min) via

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Table 1. Clinical Characteristics of Patients in the Four Study Groups

	Nonpregnant control group		Cesarean section group	
	Supine (*n* = 10)	Head-up (*n* = 10)	Supine (*n* = 10)	Head-up (*n* = 10)
Age (yr)	31.2 ± 2.9	32.7 ± 5.9	29.5 ± 4.5	28.6 ± 6.2
Weight (kg)	65.2 ± 9.1	61.9 ± 11.6	70.9 ± 12.8[a]	72.4 ± 7.0[a]
Preop So_2%	98.1 ± 1.5	98.5 ± 0.94	97.5 ± 1.3	97.9 ± 0.77
Time to So_2 95% (s)	243 ± 7.4	331 ± 7.2[b]	173 ± 4.8[a]	156 ± 2.8[a]

Preop So_2%, preoperative arterial oxygen saturation; Time to So_2 95%, time of apnea during which So_2 of 95% was reached.
Mean ± SD.
[a]Significantly different from the corresponding value in the control group.
[b]Significantly different from supine group.

the circle system of an anesthesia machine and a tight-fitting face mask over a period of 3 min. A rapid-sequence induction of anesthesia was accomplished after application of cricoid pressure using ketamine (1.5 mg/kg). Succinylcholine (1.5 mg/kg) was injected intravenously and the trachea intubated. Thereafter, the tracheal tube was left open to room air, and a succinylcholine infusion was administered to maintain apnea.

Monitoring of arterial oxygen saturation was continued throughout the period of apnea, and the time to reach 95% saturation (desaturation time) was recorded. For reasons of safety, an arterial oxygen saturation of 95% was considered our endpoint. The endotracheal tube was then connected to the anesthesia circuit and the patient's lungs were ventilated with 100% oxygen until an arterial oxygen saturation of 100% was restored. Thereafter, all patients were placed in the supine position for surgery. Anesthesia was maintained after delivery with nitrous oxide-oxygen (2:1), supplemented with vecuronium. Apgar scores of the newborns were recorded at 1 and 5 min.

Oximetry results were compared with those obtained in a control group of 20 nonpregnant women undergoing gynecologic procedures, such as hysterectomy or tubal ligation, using similar preoxygenation and anesthetic techniques. Ten of the nonpregnant control patients were studied in the supine position; the other 10 were in the 45° head-up position. (As in the pregnant group, all patients having any disease that might influence respiratory function or oxygen delivery were excluded.)

The control oxygen saturation while breathing room air, the peak saturation obtained after preoxygenation, and the mean times of apnea at which 95% saturation were reached were compared. All values were expressed as mean ± SD. The Student's *t*-test was used for statistical analysis; $P < 0.05$ was considered significant.

Results

Demographic Data

The two groups of patients were similar in age, but the mean body weight of the pregnant patients was significantly greater (Table 1). The control arterial oxygen saturation while breathing room air was not significantly different in pregnant and nonpregnant patients. After the 3 min of preoxygenation, the oxygen saturation increased to 100% in all subjects.

During apnea in the supine position, the average time to desaturation to 95% was significantly shorter in the pregnant than in the nonpregnant control patients. Use of the head-up position resulted in a significant increase in the desaturation time in the nonpregnant but not the pregnant women (Table 1). In all patients, subsequent ventilation with 100% oxygen was followed by a transient decrease in saturation to 93%–94% for 5–10 s, with a rapid increase to 100% saturation thereafter.

In the cesarean section group, all newborns had an Apgar score ≥7 at 1 min and ≥8 at 5 min.

Discussion

The present study shows that desaturation after preoxygenation occurred more rapidly in apneic pregnant than in nonpregnant women, whether positioned in the supine or the 45° head-up tilt position. In the cesarean section group, the mean desaturation time to 95% was 173 ± 4.8 s in the supine position and 156 ± 2.8 s in the head-up position, a nonsignificant difference. In contrast, the desaturation time in the nonpregnant women increased from 243 ± 7.4 s in the supine position to 331 ± 7.2 s in the head-up position.

During pregnancy, the decrease in FRC (4) results in a reduction in oxygen reserve that is compounded by the increased oxygen consumption (5). During apnea, the oxygen reserve in the FRC will be exhausted more quickly in the pregnant than in the nonpregnant woman. Similarly, in obese patients arterial desaturation is significantly faster than in normal patients, with a linear correlation between time to desaturation and degree of obesity (9,10). In obese patients, the FRC is further reduced in the supine position (11).

Our data also show that preoxygenation in the head-up position resulted in an increase of the safe duration of apnea in nonpregnant patients but was not associated with any significant change in pregnant patients. These results were unexpected, because a change from the supine to the sitting position has been shown to increase the FRC in both the pregnant (4) and nonpregnant patient (12). It is possible that adopting the 45° head-up rather than the sitting position may not significantly increase the FRC in the pregnant patient at term. In contrast, the FRC may significantly increase with position change in the nonpregnant woman, because most of the alteration in FRC takes place between the horizontal and 60° head-up tilt position (12).

In conclusion, the present study shows that after 3 min of preoxygenation, desaturation during subsequent apnea, as monitored by pulse oximetry, is more rapid in pregnant than in nonpregnant patients. Changing from the supine to the 45° head-up position prolongs the desaturation time in the nonpregnant patient but has no effect in the pregnant woman.

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Metoclopramide-Enhanced Analgesia for Prostaglandin-Induced Termination of Pregnancy

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We previously determined that a single dose of metoclopramide could significantly reduce the patient-controlled analgesia (PCA) morphine requirements of women undergoing prostaglandin-induced termination of pregnancy. In the present study, we evaluated whether repeated doses of metoclopramide would further reduce pain and accelerate expulsion of the fetus. After intraamnionic injection of prostaglandin, patients were randomly allocated to receive either 10 mg of intravenous metoclopramide (n = 17) or saline (n = 15), concurrent with the initiation of PCA. A second, identical dose was administered 4 h later. Data included visual analogue scale scores for pain 45 min after each administration of metoclopramide or saline and visual analogue scale and sedation scores every 2 h for the first 10 h, amount of morphine delivered by PCA pump, time of fetal and placental passage, and hospital discharge. Metoclopramide-treated patients experienced significantly earlier fetal and placental passage ($P < 0.05$). This was associated with a 66% reduction in PCA morphine received by the time of fetal delivery ($P < 0.05$). In addition, patients in the metoclopramide group were discharged from the hospital significantly sooner ($P < 0.05$). This difference included fewer second-day hospital stays ($P < 0.05$). Visual analogue scale scores measured 45 min after each infusion of the study agent were reduced from baseline in the metoclopramide group only ($P < 0.05$). No significant intergroup differences were noted with respect to pain or interval morphine usage. We conclude that repeated doses of metoclopramide significantly reduce the duration of induced labor and therefore the total PCA morphine requirements. This effected an earlier hospital discharge for patients undergoing prostaglandin-induced labor. The analgesic potentiating effect of metoclopramide is demonstrable within 45 min of administration.

(Anesth Analg 1992;75:760–3)

In a preliminary trial, we determined that the intravenous administration of metoclopramide significantly reduced the intravenous patient-controlled analgesia (PCA) opioid requirements and early pain scores of women undergoing induced labor for termination of pregnancy (1). In addition, the time interval between the intraamnionic injection of prostaglandin $F_{2\alpha}$ and fetal passage was significantly shortened.

Our use of metoclopramide for the purpose of reducing pain in this patient population was prompted by reports that metoclopramide provides effective analgesia for renal colic and improves analgesia when used for the treatment of opioid-induced nausea during labor (2–4). The effect of metoclopramide in the genitourinary tract may be attributed in part to its antagonism of the dopamine receptor and to its cholinergic activity, reducing smooth muscle spasm and increasing effective peristaltic action (5). Dopamine has also been demonstrated to depress the peristaltic activity of the fallopian tubes in an animal model (6). In addition, intravenous metoclopramide is capable of stimulating the neuroendocrine axis (7–9).

We repeated our trial with the use of two intravenous doses of metoclopramide, separated by 4 h, to determine whether by maintaining the level of metoclopramide we could extend the period of improved analgesia, promote passage of the placenta, and accelerate hospital discharge.

Methods

The study was approved by our Human Investigation Committee, and informed, written consent was obtained from 37 adult women, ASA physical status II, who had elected to have their second-trimester preg-

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nancies terminated by an intrauterine injection of prostaglandin $F_{2\alpha}$ (Hemabate). Subjects were instructed in the use of a PCA device (Abbott Life Care II) and in the use of a visual analogue scale (VAS) for pain (0 = no pain; 10 = worst possible pain). They were randomly allocated in a double-blind fashion to receive either intravenous metoclopramide (10 mg) or an equivalent volume of normal saline when a VAS score of >5 was achieved. Patient-controlled analgesia (1 mg of morphine every 6 min on demand and a constant infusion of 1 mg/h) was begun 10 min after the study agent was administered. The dose of metoclopramide or saline was repeated 4 h later. Antiemetic medication (droperidol) and prostaglandin E suppositories needed to enhance labor were administered as per established hospital protocol.

The following data were collected by a nurse-investigator: VAS scores 45 min after each intravenous administration of metoclopramide or normal saline and VAS and sedation scores (graded from 1 = alert and oriented to 5 = stupor) every 2 h for the first 10 h, amount of PCA morphine delivered, time of fetal and placental passage, and hospital discharge. Differences between the groups with respect to VAS scores were analyzed using the Wilcoxon rank sum test. Differences in morphine consumption were analyzed with unpaired *t*-test and two-factor analysis of variance for repeated measures. Summary variables, including demographics, were analyzed using unpaired *t*-test and Fisher's exact test. A *P* value <0.05 was considered statistically significant.

Results

Of the 37 patients studied, 5 were not included in the analysis because of incomplete PCA data. Of the remaining subjects, 17 received metoclopramide and 15 normal saline. The two groups were similar with regard to age, weight, parity, surgical history, gestational age, reason for choosing termination of pregnancy, and baseline pain. After intravenous drug administration, interval sedation scores, doses of antiemetic medication, and number of prostaglandin E suppositories needed to enhance labor did not differ between groups. There were no untoward effects noted.

Forty-five minutes after each injection of metoclopramide or saline, only the metoclopramide-treated patients reported a significant reduction in the VAS score for pain ($P < 0.05$) (Figure 1). Two-hourly VAS scores for pain did not differ significantly between groups.

Likewise, interval morphine use did not differ significantly between groups. However, patients in the metoclopramide group received 66% less total morphine until passage of the fetus (12.2 ± 8.5 vs 27.6 ± 20.3 mg [mean ± SD]) ($P < 0.05$). This reduce total morphine requirement reflects significantly ea lier fetal expulsion (3.12 ± 2.8 vs 6.63 ± 5.7 h) ($P <$ 0.05) (Figure 2). Placental passage occurred signif cantly earlier in the metoclopramide-treated grou (4.56 ± 3.3 vs 8.74 ± 5.7 h) ($P < 0.05$) (Figure 2).

Moreover, patients treated with metoclopramid experienced earlier hospital discharge (12.0 ± 7.5 v 21.25 ± 6.2 h) ($P < 0.05$) (Figure 2). This differenc

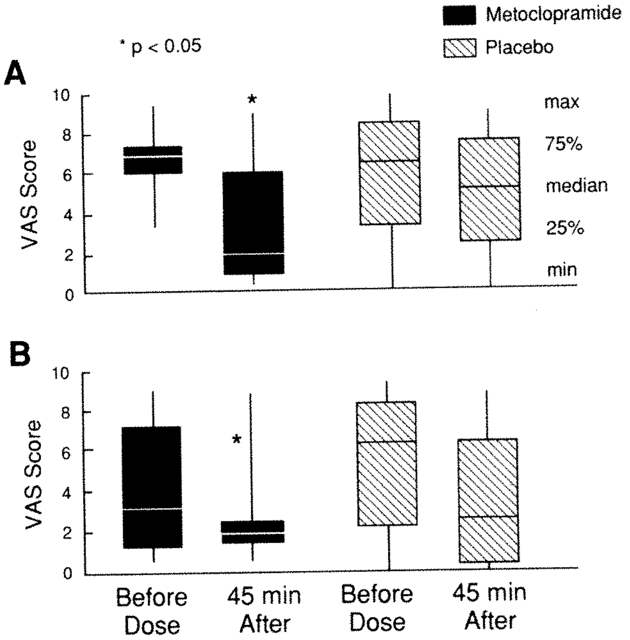

Figure 1. Visual analogue scale (VAS) scores before and 45 min after the first (**A**) and second (**B**) administration of metoclopramide or normal saline. *Significant intragroup change in VAS.

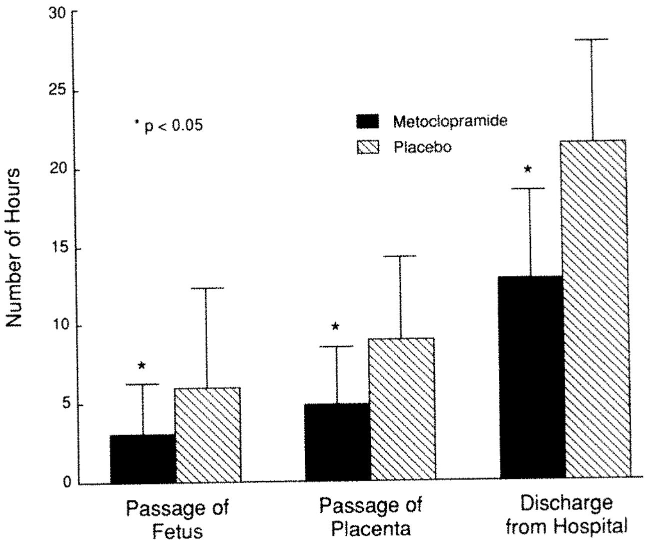

Figure 2. Time from first dose of metoclopramide or normal salin (and start of patient-controlled analgesia) to events of fetal an placental expulsion and hospital discharge.

included significantly fewer second-day hospitalizations (5 vs 11 in the saline-treated group) ($P < 0.05$). Sedation scores were not significantly different, but placebo-treated patients tended to be more sedated at the latest hour of observation ($P = 0.1$).

Discussion

These data are consistent with findings in our preliminary study in that metoclopramide treatment was associated with a reduction in the duration of induced labor and hence total demand-analgesic requirements. In addition, we now have demonstrated a sharp reduction in pain scores, accelerated fetal and placental passage, and earlier hospital discharge. Although sedation scores did not differ significantly, higher scores did occur in the tenth hour of study in the placebo-treated patients. This may in part explain the later hospital discharge of this group, owing to the sedative effects of their greater total morphine intake and exhaustion due to a prolonged labor. Exact discharge criteria were based on the "home-ready" evaluation by the gynecology nursing staff.

Metoclopramide is a central and peripheral dopamine antagonist with peripheral cholinergic properties. It has been noted to oppose the gastrointestinal inhibitory effects of the specific dopamine agonist, apomorphine, and to accelerate gastric emptying and intestinal peristalsis (10). Recently, metoclopramide has been found to have investigative and therapeutic applications in urology (2,3,5).

In the present study, metoclopramide was associated with a significant but short-lived reduction in the pain associated with prostaglandin-induced labor. Furthermore, there was an accelerated delivery of the abortus.

We speculate that the cramping pain of prostaglandin-induced labor may be due to incoordinate muscular contraction of the fallopian tubes (i.e., spasm). As in the gastrointestinal and urinary tracts, metoclopramide may restore normal peristaltic function to this smooth muscle system, thereby reducing the discomfort at its source and providing an improved expulsive force. There is evidence to suggest such a role for dopamine receptor antagonism in this setting: (a) dopamine receptors have been identified along the length of the human fallopian tube, and the in vitro application of dopamine in the sow oviduct has been shown to depress normal peristaltic activity (8,11); (b) metoclopramide stimulates human ureteral peristalsis and canine detrusor and urethral sphincter activity (3,12); (c) clinically, metoclopramide is efficacious in the treatment of renal colic (2,5); and (d) a previously reported incidental finding of Vella et al. (4) was that patients receiving meperidine and metoclopramide (for antiemetic therapy) during spontaneous labor had significantly lower pain scores than those receiving meperidine and promethazine.

The shortening of the time to passage of the fetus in the metoclopramide-treated group may have a central neuroendocrine mechanism. Metoclopramide (10 mg) is capable of stimulating the neuroendocrine axis, as is noted in human studies in which prolactin and vasopressin release are increased (8). It is possible that, like other dopamine antagonists, metoclopramide facilitates oxytocin release, thus enhancing uterine activity (13). However, the effect of dopamine and dopamine agonists is not consistent throughout the course of pregnancy, and one can only speculate as to the application of this effect to term labor.

It should be noted that the present study differs from our previous one not only in that the current protocol included a second dose of metoclopramide, but also in the course of the control patients: although the interval from intraamniotic injection of prostaglandin $F_{2\alpha}$ to onset of significant cramping pain was similar in both study populations (2–2.5 h), all patients in the current study had significantly higher baseline VAS scores before receiving metoclopramide or saline compared with the earlier study (6.4 vs 4.8) ($P < 0.05$). In addition, the current control patients expelled the fetus significantly earlier than their control counterparts in the earlier study (9.1 vs 15.7 h) ($P < 0.05$). This is not immediately explainable, in that there were no apparent differences between the two study groups with regard to the protocol for induction of labor. These baseline differences confound any attempt at close comparison of the two study populations.

In conclusion, the present data indicate that two doses of metoclopramide administered at an interval of 4 h effectively shortened the duration of induced labor (and hence reduced total PCA morphine consumption) and duration of hospitalization. In addition, acute relief of pain was noted. However, the decrease in pain was not sustained in that the metoclopramide-treated and control populations experienced similar overall VAS scores. By reducing overall cumulative morphine consumption, metoclopramide may have reduced sedation and allowed earlier hospital discharge.

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Comparison of Methods for the Detection of Myocardial schemia During Noncardiac Surgery: Automated T-Segment Analysis Systems, Electrocardiography, and ransesophageal Echocardiography

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Clinicians often fail to detect intraoperative ischemic electrocardiographic (ECG) changes when viewing oscilloscopes. Automated ST-segment monitors promise to increase the detection of such ECG changes. We investigated the capacity of two commercially available ST-segment monitors to detect intraoperative myocardial ischemia in patients at high risk for developing intraoperative myocardial ischemia during vascular and other noncardiac procedures. The ST-segment monitors were compared with two reference monitors: (a) printed eight-lead ECGs, as interpreted by a cardiologist, and (b) the presence of segmental wall motion abnormalities and thickening abnormalities detected by transesophageal echocardiography (TEE). We also examined the capacity of the printed ECG to diagnose myocardial ischemia when compared with TEE. We studied 44 patients who underwent TEE, printed multilead ECG, oscilloscope monitoring of leads V_5 and II, and measurement of ST-segment deviation from the baseline using an automated Hewlett Packard ST-segment device. The sensitivities for the Hewlett Packard system were 40% for TEE-diagnosed myocardial ischemia and 75% for ECG-diagnosed ischemia. Comparison of the printed ECG with TEE revealed that ST-segment changes in the printed ECG, as analyzed by a cardiologist, were 25% sensitive and 62% specific for the detection of TEE-diagnosed myocardial ischemia. When T-wave inversions were added to ST-segment depression as a criterion for the diagnosis of myocardial ischemia by the printed ECG, the sensitivity of ECG for the detection of intraoperative myocardial ischemia, as determined by TEE, was 40% and specificity was 58%. Twenty-three of the 44 patients were simultaneously monitored in leads I, II, and V_5 with an automated Marquette ST-segment monitor. In the 23 patients monitored with both Hewlett Packard and Marquette systems, the sensitivities (80% vs 100%, respectively) and specificities (67% vs 50%, respectively) were similar for ECG-diagnosed myocardial ischemia. Monitors of intraoperative myocardial ischemia often do not agree with each other; however, automated ST-segment monitors predict most ischemic changes seen on the printed ECG and can be used as an alarm to alert the clinician to examine the ECG.

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Recent work has documented the high incidence of perioperative ischemia in patients with peripheral vascular disease (1) and in those with nown coronary artery disease (2). In patients undering coronary artery bypass grafting procedures, rioperative myocardial ischemia has been associed with an increased risk of perioperative myocardial infarction (3). In patients undergoing noncardiac surgery, ST-segment depression detected by Holter monitoring after surgery predicts a ninefold increase in the risk of ischemic postoperative events (4). Because myocardial ischemia is often not detected by clinicians when viewing oscilloscopes (5), automated vigilance of the ST segments of the electrocardiogram (ECG) has been proposed as a method to alert clinicians to changes in the ECG (6,7).

Several instruments that continuously monitor deviation of the ST segment at a defined point in the cardiac cycle are now available. Although this technology has been used to define demographic predic-

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tors of intraoperative myocardial ischemia (8), ST-segment monitors have not been compared directly with other established techniques for the detection of intraoperative myocardial ischemia.

The goal of this study was to assess this new ST-segment monitoring technology. Accordingly, we tested the hypothesis that ST-segment trend analysis could detect intraoperative ischemia as well as two commonly used techniques: (a) analysis of printed multilead ECG by a cardiologist, and (b) the detection of abnormalities in wall motion using two-dimensional transesophageal echocardiography (TEE). We compared two ST-segment trend monitors with ECG and TEE detection of intraoperative myocardial ischemia to determine sensitivity, specificity, positive predictive rate, and negative predictive rate for the two ST-segment trend monitors. In determining these rates, printed ECG and TEE were considered as standard reference monitors.

The need for determining these four rates when assessing new technology has been recently highlighted by Cooper et al. (9) who, in decrying the poor quality of early evaluations of magnetic resonance imaging, noted that "sound and scientifically rigorous evaluation of new technologies is necessary to insure quality of care and cost-effective use of resources." Rigorous technology assessment is crucial, for an unproved technology may not only prove costly, but may also delude the clinician into believing a sick patient normal or into initiating treatment when none is needed.

Methods

Patient Selection and Measurement Periods

After Institutional Review Board approval and patient consent, we studied 44 patients whose mean (±SD) age was 64 ± 12 yr. Of these 44, 35 underwent vascular reconstructive surgery (16 aortic, 12 carotid, and 7 femoral artery procedures). Nine other patients with significant risk factors for coronary artery disease undergoing other types of noncardiac surgery were also studied. Five were studied during laparotomy, and the remaining four underwent miscellaneous procedures. Those included in our study had at least two of the following risk factors: (a) age >70 yr, (b) history of hypertension, (c) history of peripheral vascular disease, (d) history of diabetes, (e) chronic renal failure, or (f) known coronary artery disease. The only exclusion criteria used were the presence of left bundle branch block pattern, a ventricular paced rhythm, or cardiac surgery. Left ventricular hypertrophy with "strain pattern" on ECG was not considered an exclusion. The ECGs were printed and ST-segment data recorded at 5 min before and after induction of anesthesia and at 5 min after tracheal intubation. Complete measurements (ECG, ST segments, and TEE) were carried out for 15 s before and after incision and 5 min before and after vascular occlusion and reperfusion during major vascular surgery, whenever any of the monitors suggested myocardial ischemia or whenever major hemodynamic perturbations (≥40% change from baseline in heart rate or mean arterial blood pressure) occurred.

ST-Segment Trend Monitors

To each patient we applied the leads of one or both of two ST-segment monitors. The Hewlett Packard (HP) (Hewlett Packard, Waltham, Mass.) 78534C monitor was used in all 44 patients. This monitor measured the deviation of the ST segment at a point 120 ms after the R wave from a baseline defined at 80 ms before the R wave. Paced beats were discarded and the median value during a 15-s epoch displayed. These recordings were made in the diagnostic mode, within the frequency 0.05–100 Hz. The value of ST-segment deviation was measured in leads II and V_5; the absolute values of ST-segment variation in these two leads were summed and displayed by the monitor.

The ST-segment monitors display a total that represents the sum of the absolute values of ST-segment change in the monitored leads. Therefore, we prospectively defined myocardial ischemia as the increase of 1.0 mm in the sum of the absolute value of ST-segment score over the lowest absolute value (closest to no deviation) measured during the operative procedure. We assumed that most ischemic changes would be in one vascular bed and, therefore, in one lead at a time. The definition of myocardial ischemia as 1 mm or greater change in the summated leads is not standard. However, we chose this definition in an attempt to improve sensitivity and also because this summed presentation is the usual manner in which the monitor displays data to the clinician.

A second monitor, the Marquette (MQ) (Marquette, Milwaukee, Wis.) 7000 ST-segment trend monitor, was applied simultaneously to 23 of the patients in the HP group. This monitor became available after we began our studies with the HP system. The MQ monitor measured the ST segment at 80 ms after the J point in leads I, II, and V_5, and summed the absolute values of ST-segment deviation from the baseline in the three leads. The monitor was used in a diagnostic mode, with a frequency response of 0.05–40 Hz. We prospectively defined myocardial ischemia as the increase of 1.0 mm over the lowest ST-segment sum during the case. When two ECG onitors (HP and MQ) were applied, the electrodes ere cut and attached so as to make them adjacent to ch other for the same lead on different machines. e were aware that results obtained from the HP and Q monitors might vary, because the HP monitor d not use a J-point reference. In addition, the MQ stem used an additional lead (I). Neither of the -segment systems tested allowed adjustment of the int in the cardiac cycle at which the isoelectric seline or the ST segment was measured.

wo-Dimensional Transesophageal Echocardiography

TEE probe was placed in each of the 44 patients ortly after induction of anesthesia. Short-axis views the midpapillary muscle level were recorded for s simultaneously with ST-segment trend and ECG ta, except for the period preceding tracheal intuba- n, when TEE was unavailable. The echocardio- ams were read by a single cardiologist unaware of e clinical condition; wall motion in each of four adrants was graded as 1 = normal, 2 = mild pokinesis and thickening abnormality, 3 = moder- e hypokinesis and thickening abnormality, 4 = inesis and lack of thickening, 5 = dyskinesis. An crease in the wall motion score of 2 or greater was e definition of myocardial ischemia as detected by E. The baseline for each quadrant was considered be the lowest score noted during TEE monitoring, t necessarily the initial TEE recorded after induc- n.

lectrocardiograms

e ECGs of all 44 patients were monitored with a ve-cable system that allowed printing of the six limb ads (I, II, III, aVR, aVL, aVF), the V_5 lead, and the CL_1 lead. These eight leads were printed at the me time that TEE images were recorded on video- pe: (a) on arrival in the operating room, (b) before d after intubation (when TEE was unavailable),) before and after vessel occlusion and reperfusion long with TEE), (d) whenever any of the modalities ggested myocardial ischemia (along with TEE), and) when there were hemodynamic perturbations as eviously defined (along with TEE). These ECGs ere reviewed by a second, independent cardiologist r the presence of myocardial ischemia; she was aware of clinical conditions. Our prospective defi- tion of myocardial ischemia on the printed ECG as 1.0 mm of downsloping ST-segment depression ver the minimal value in any one lead or T-wave versions occurring in more than one lead, or both. he ECG tracings for all 44 patients were available for alysis.

Table 1. Definitions of Rates Used in Technology Assessment

Technology in question (test)	Reference standard (disease) +	Reference standard (disease) −
+	A	B
−	C	D

Sensitivity = Positive test in disease = A/(A+C).
Specificity = Negative test in health = D/(B+D).
Positive predictive value = Disease with a positive test = A/(A+B).
Negative predictive value = Healthy with a negative test = D/(C+D).

Statistical Considerations

To determine the efficacy of the new technology, we compared it with accepted technologies and definitions of the disease state. To define sensitivity (how often the test is positive when the reference standard says the patient has the disease) and specificity (how often the test is negative when the reference standard says the patient does not have the disease), we first needed to define a reference standard. The TEE and eight-lead ECGs were used as two clinically available, separate arbitrary reference standards for the definition of intraoperative myocardial ischemia.

We pooled all periods of time for each patient so that any reading of myocardial ischemia detected during the patient's procedure resulted in that patient being considered to have had an ischemic event. Normal readings at all time periods were taken to indicate the absence of ischemia. Therefore, we determined how well the different ischemia-detection monitors predicted ischemia during an operation, not at each episode. Furthermore, we believe that pooling was necessary because of the different time frames after an ischemic episode in which each monitor is capable of revealing ischemia (10). However, we did note the incidence of ischemic ECG changes that occurred before placement of the TEE probe (i.e., during the stresses of induction, laryngoscopy, and tracheal intubation).

In addition, the positive predictive rate (the percentage of patients with an abnormal test who truly have the disease) and the negative predictive rate (the percentage of patients with a negative test who are truly healthy) were computed (Table 1).

Results

Hewlett Packard ST-Segment Monitors Versus Transesophageal Echocardiography as the Reference Standard

Forty-four patients had both HP ST-segment scores and TEE images available for comparison of the two

Table 2. Sensitivity and Specificity of Ischemia Detection Methods

	Arbitrary reference standard				
				ECG	
Test	TEE	HP	MQ	ST segment	ST segment + T-wave changes
TEE ($n = 44$)	×	Sens:47% Spec:56%	Sens:50% Spec:78%	Sens:62% Spec:58%	Sens:67% Spec:62%
HP ($n = 44$)	Sens:40% Spec:63%	×	Sens:43% Spec:75%	Sens:75% Spec:69%	Sens:50% Spec:68%
MQ ($n = 23$)	Sens:78% Spec:50%	Sens:80% Spec:54%	×	Sens:100% Spec:50%	Sens:83% Spec:47%
ECG (ST segment) ($n = 44$)	Sens:25% Spec:62%	Sens:35% Spec:93%	Sens:36% Spec:100%	×	Sens:67% Spec:100%
ECG (ST segment or T-wave changes, or both) ($n = 44$)	Sens:40% Spec:58%	Sens:35% Spec:78%	Sens:64% Spec:89%	Sens:100% Spec:89%	×

TEE, transesophageal echocardiography; HP, Hewlett Packard; MQ, Marquette; ECG, electrocardiogram; Sens, sensitivity; Spec, specificity.

modalities. When TEE was used as the reference standard of myocardial ischemia, the sensitivity of the HP system was found to be 40%. In the 20 patients with TEE ischemia, only 8 (40%) had an ST-segment score change of ≥1.0 mm. The specificity of the HP system was 63%; of 24 patients without a significant wall motion abnormality, 15 were without a 1.0-mm increase in their ST-segment score. The positive predictive rate was 47%; of 17 patients with a ≥1.0-mm change in their ST-segment score, 8 had significant wall motion abnormalities by TEE. Finally, the negative predictive rate was 56%; of the 27 patients without ischemia by ST-segment analysis, 15 were without significant wall motion abnormality.

ST-Segment Monitors Versus Electrocardiography as the Reference Standard

In all 44 patients with ECG strips, the HP ST-segment device was compared with the reference standard of ST-segment changes on the printed ECG interpreted by a cardiologist. The sensitivity of the HP ST-segment monitor was 75% (6 of 8), the specificity 69% (25 of 36), the positive predictive rate 35%, and the negative predictive rate 93% compared with the printed ECG.

In the 23 patients in whom both the MQ and HP monitors were simultaneously applied, we also used the cardiologist's interpretation of the ST segments from the printed ECG as the reference standard for ischemia. Our results showed that the HP system was 80% (4 of 5) sensitive and 67% (12 of 18) specific, with a positive predictive rate of 40% (4 of 10) and a negative predictive rate of 92% (12 of 13). The MQ system demonstrated a sensitivity of 100% (5 of 5) and specificity of 50% (9 of 18), with a positive predictive rate of 36% (5 of 14) and a negative predictive rate of 100% (9 of 9) (Table 2).

Printed Electrocardiography Versus Transesophageal Echocardiography as the Reference Standard

In the group of 44 patients, we determined the sensitivity of the printed ECG using TEE as our reference standard for ischemia detection. We examined ST-segment changes, both with and without T-wave inversions, in addition to the presence of isolated T-wave changes, to compute sensitivities and other indices of accuracy. When TEE was considered the comparison standard, sensitivity of ST-segment changes in the printed ECG was 25% (5 of 20), specificity 62% (15 of 24), positive predictive value 62% (5 of 8), and negative predictive rate 58% (21 of 36) (Table 2). When T-wave criteria were added to the definition of ischemia on the printed ECG, sensitivity increased to 40% (8 of 20), whereas specificity was 58% (14 of 24) (Table 2). For an isolated T-wave change, compared with TEE, the positive predictive value was 75% (i.e., three of four patients with isolated T-wave inversions had an ischemic TEE).

Timing of Ischemic Episodes

We also examined how often ECG changes occurred before insertion of the TEE probe. Three patients developed ischemia, as detected by ST-segment changes in the printed ECG before placement of the TEE probe; all three demonstrated subsequent evidence of ischemia as detected by TEE.

Myocardial ischemia occurred most commonly during defined periods of expected stress, such as intubation, incision, and vascular occlusion. Thirty-

Table 3. Comparison of the Incidence of Ischemic ST-Segment Changes in Patients With and Without Left Ventricular Hypertrophy on Preoperative Electrocardiogram

	Patients with LVH	Patients without LVH
Intraoperative ECG ischemia	1	7
No intraoperative ECG ischemia	8	28

LVH, left ventricular hypertrophy; ECG, electrocardiogram.
$\chi^2 = 0.380$; 10% critical value = 2.706 (no significant difference).

two of the patients demonstrated myocardial ischemia by one or more of the modalities. Thirty of these 32 patients (94%) demonstrated ischemia during the defined sampling periods, whereas 15 of the 30 also had ischemia during additional time periods. Only two patients had ischemia only during the additional time periods in which measurements were made during abnormal hemodynamics, without manifesting ischemia during expected periods of stress. In these two patients, ischemia was detected by TEE and T-wave inversions in one and by ST-segment changes in the other.

Effects of Left Ventricular Hypertrophy on Incidence of Ischemia Diagnosed by Printed Electrocardiography

We did not exclude patients who had left ventricular hypertrophy (LVH) from this study, although the presence of LVH with repolarization changes ("strain") may make the diagnosis of myocardial ischemia by ECG difficult. The preoperative ECGs of all 44 patients were reviewed for the presence of LVH. Thirty-five patients did not have LVH, seven patients had LVH by voltage criteria without repolarization changes, and only two had LVH with repolarization changes. Neither of the patients with LVH with strain had intraoperative ST-segment changes of >1 mm. A comparison of the incidence of ischemic ST-segment changes in patients with and without LVH appears in Table 3; there was no significant difference.

Intraobserver Variability of Transesophageal Echocardiographic Readings

The videotaped echocardiographic recordings of 16 patients were analyzed 1 yr later by the same reviewer to establish intraobserver variability. In 10 of 16 (62%) patients reviewed, the observer agreed with his previous determination of the presence or absence of intraoperative myocardial ischemia. Five of the six patients who had discordant determinations had small disagreements: (a) a change from normal to moderate hypokinesia read originally was later called a change to mild hypokinesis (four patients; all changed from a two-grade change to a one-grade change); and (b) a change from normal to moderate hypokinesia read originally was later called no change (one patient; a two-grade change). In one patient with baseline segmental wall motion abnormalities (SWMAs), the original reading detected no decrease in function, whereas repeat reading detected a change from moderate hypokinesia to dyskinesia (two-grade change). In 68 of the 88 (77%) episodes reviewed in these 16 patients, the observer agreed with the diagnosis of a normal or ischemic episode.

Discussion

Recent work has highlighted the common and deleterious, yet often unrecognized, nature of perioperative myocardial ischemia (4). Printed ECG and TEE may be used, but they are discontinuous and require physician attention. The use of automated ST-segment monitors has been reported to assist in the vigilance of anesthesiologists (5–7). Although such monitors have been used to document ischemia occurring during reported cases (5) and to define demographic risk factors for the development of intraoperative ischemia during cardiac surgery (7), ST-segment analysis has not been compared with other methods of detecting intraoperative myocardial ischemia.

Limitations of This Study

We used intermittent, brief recordings of TEE and printed ECG in this study. Therefore, it is possible that we missed other periods of ischemia. However, we studied patients during periods of operative stress, such as tracheal intubation and aortic occlusion, and during hemodynamic stress when we believed that ischemia would be the most likely to occur. When we sampled data at times other than the defined perioperative events (during hemodynamic abnormalities or suspected myocardial ischemia), it added little to the detection of ischemia: only two patients, for example, had ischemia detected during periods other than the defined perioperative events. The 18% incidence of myocardial ischemia (detected by ST-segment changes in intermittent printed ECG) in our patients is similar to that reported by other workers who have used continuous ECG monitoring during vascular surgery (11). We therefore believe that such an incidence of myocardial ischemia allows the comparison of the different detection modalities.

We decided to analyze our data by comparing the evidence of ischemia detected during an operation by each monitoring modality rather than by comparing corresponding episodes. We pooled our data because of the temporal dissociation of ECG and TEE in detecting intraoperative myocardial ischemia. This temporal dissociation of ECG and TEE in detecting intraoperative myocardial ischemia has recently been demonstrated by London et al. (12). In that study, although 19 patients had ischemia detected by both modalities, simultaneous ischemia was detected in only 5 patients (12).

Limitations of Transesophageal Echocardiography in Detecting Myocardial Ischemia

A major limitation of TEE is its inability to monitor patients during one of the most stressful parts of surgery—tracheal intubation. Although TEE may be used in awake patients, insertion of the probe before induction of anesthesia might be uncomfortable and might produce additional stress in the patient; it would certainly complicate airway management. Transesophageal echocardiography was not available to us during induction of anesthesia and intubation of the trachea; however, all three of the patients who had ST-segment changes on ECG as evidence of ischemia during this period subsequently developed an ischemic TEE study during surgery.

Transesophageal echocardiography has at least three other limitations in its capacity to detect intraoperative myocardial ischemia. First, although the short-axis view at the midpapillary muscle level does demonstrate the mechanical function of regions subserved by all three major coronary arteries, this view will not detect apical abnormalities. Chung et al. (13) reported a patient who had an anteroapical myocardial infarction (documented by transthoracic echocardiography) after aortocoronary bypass, who demonstrated ST-segment elevation during surgery but whose TEE remained unchanged. As a corollary, it is also possible that if a patient has an apical scar, and the echocardiographer is not careful to maintain a short-axis view at exactly the same level, moving the view in and out of the area of scar may cause the false diagnosis of myocardial ischemia to be made. Second, it has been suggested that changes in afterload, rather than myocardial ischemia, can produce regional wall motion abnormalities. Kavanaugh et al. (14) found in a dog model that the area of wall motion abnormality produced by coronary artery occlusion indeed was greater than was the area of hypoperfusion; however, in that study, pharmacologically induced changes in afterload did not alter segmental wall motion. Third, the normal heart does not have homogeneous contractility; in canine experiments, the apex of the heart has been shown to have greater systolic shortening than basal regions of the left ventricle (15). In those experiments, performed without coronary artery constriction, the differences in regional systolic shortening were statistically significant. However, it is not clear whether the regional heterogeneity was great enough that it would be confused with myocardial ischemia. For example, when dogs were anesthetized with 1% isoflurane, percent systolic shortening was 18% in the apex and 13% in the base; the addition of verapamil abolished the difference in percent systolic shortening, decreasing them to 10% and 9% respectively. It is unlikely that the change from 18% to 10% in the apex would be called hypokinetic relative to the change in the base (13% to 9%). Indeed, the apex is not routinely monitored with TEE. Lowenstein et al. (16), in a recent editorial, discussed animal work in which afterload was increased after a period of myocardial ischemia (17). They point out that although increased afterload does diminish systolic shortening in postischemic myocardium, the decrease does not appear to be of the magnitude that would be associated with a new SWMA. This lack of change would be even less likely to be considered a SWMA when thickening changes are also considered a criteria for SWMA diagnosis, as we believe necessary. Further work is clearly needed to define the sensitivity and specificity of TEE in detecting myocardial ischemia, particularly in the settings of "stunned" myocardium and varying afterload.

We found a disturbingly high intraobserver variability in the diagnosis of myocardial ischemia. In 16 patients in whom studies were reviewed twice, 1 yr apart, 5 patients had a change in diagnosis of intraoperative ischemia. Four of the five patients had a change from normal to moderate hypokinesis, later called a change to mild hypokinesis. We now believe that a change to moderate hypokinesis, which we prospectively defined as change that might represent myocardial ischemia, may not be so significant a change. Tischler et al. (18), using dipyridamole echocardiography to evaluate patients before vascular surgery, scored segments as normal, hypokinetic, akinetic, or dyskinetic; they required a change of one grade to diagnose ischemia. London et al. (12) scored segments as normal, mild hypokinesis, severe hypokinesis, akinesis, or dyskinesis; they required a change of two grades (i.e., from normal to severe hypokinesis) to define a SWMA as representative of myocardial ischemia. Even with these more stringent criteria, the detection of new severe hypokinesis did not appear to herald adverse outcome. The changes that we detected from normal to moderate hypokinesis may represent trivial episodes of myocardial ischemia, or not even myocardial ischemia at all.

ST-Segment Devices

When the HP ST-segment monitor results were compared with analysis of ST-segment changes in the printed ECG for each of the 44 patients, reasonable correlations were seen. The predictive negative rate was an impressive 93%; that is, when the ST-segment monitor never increased its score by ≥1.0 mm, only 7% of the patients developed intraoperative myocardial ischemia, as indicated by printed ECG ST-segment changes. In the smaller group of 23 patients monitored with both MQ and HP monitors, the additional use of lead I in the MQ system was associated with a somewhat greater sensitivity (100% vs 80%) and somewhat lower specificity (50% vs 67%). This finding is surprising, because the extra lead used by the MQ, lead I, is rarely associated with intraoperative ischemic changes, as has been demonstrated by London et al. (19). The lower positive predictive values of both devices suggest that they detect ST-segment change more often than does a cardiologist's interpretation, for potential reasons that are discussed later. Although it would be possible to compare the individual leads used to calculate the ST-segment sum with other standards for diagnosing ischemia, such would not be an appropriate technology assessment, because it is the sum of changes that the clinician is presented with to make decisions. Thus, we believed that the appropriate technology assessment utilized sums for comparisons.

Limitations of ST-Segment Devices

The automated ST-segment monitors have various technical limitations that may produce erroneous results. They do not adjust the isoelectric point or the point in the ST segment at which ischemic changes are measured during tachycardia, nor do they distinguish upsloping or downsloping ST segments. Although the isoelectric baseline of the HP device was always chosen at 80 ms before the R wave, the MQ algorithm was not available to us. The difference between the detection algorithms of HP and MQ might be highlighted by tachycardia, which may produce erroneous determinations of ST-segment changes. Tachycardia is associated with a shortened PR interval, a taller P wave, and deflection of the PQ segment below the isoelectric line (20). Using fixed (relative to the QRS complex) points for the isoelectric point may either cause the isoelectric point to be measured in the P wave, causing a normal ST segment to appear falsely depressed in comparison, or to be measured during a PR segment that is deflected below the isoelectric line.

False-positive determinations of myocardial ischemia by automated ST-segment devices may also be due to inaccurate measurement of the ST segment. It is not clear how the HP system's lack of a J-point reference affects results. For both systems, however, tachycardia may shorten the ST segment (21); measuring the ST segment at a fixed time of 120 ms after the height of the R wave (as is done by the HP system) may result in the "ST segment" actually being measured during the T wave. The resultant inaccuracy will depend on the polarity of that T wave. Newer improvements (which were not available to us at the time of study) in both devices allow the clinician to view with a cursor at what point in the ECG the baseline and ST-segment measurements are being made and to alter the position of that cursor. This additional capacity may lessen artifacts due to tachycardia and abnormal isoelectric baselines; however, our study did not address this hypothesis.

A comparison of the patients who were monitored with the HP and MQ monitors revealed that 8 of 23 patients had discordant results. We do not have printouts from the MQ monitor to verify its algorithm, because we recorded the values displayed on the oscilloscope. In the eight patients with discordant results, we noted that MQ was positive in six patients and HP was positive in two. This is not surprising, given the higher sensitivity of the MQ system in detecting ECG ischemia. Even in these discordant cases, the differences between the maximal intraoperative change in absolute sums in the two systems were small. The differences ranged from 0.3 to 1.6 mm. Of note, three of these discordant results (MQ positive, HP negative) occurred because the change in the MQ was exactly 1.0 mm.

Others have shown that different operating room ECG systems may vary in their capacity to detect myocardial ischemia. Slogoff et al. (22) have recently demonstrated that ECG systems may vary in the amount of ST-segment change detected in patients undergoing coronary artery bypass graft surgery. Some of these differences appear to be due to the use of 0.5 Hz as the lower end of the frequency response range for many operating room monitors. In such cases, the use of the monitoring mode increases the incidence of myocardial ischemia (ST-segment changes of >1.0 mm) seen in coronary artery bypass graft surgery patients before cardiopulmonary bypass. Although 8.3% of patients demonstrated ischemia by these criteria in lead V_5 on a Holter monitor, and 12.8% of patients demonstrated ischemia by these criteria on a standard 12-lead ECG, the incidence of ischemia detected by an operating room monitor in that study was 27.5% (22). This high figure is probably due to artifactual ST-segment depression caused by the 0.5-Hz filter. In our study, the printed ECGs were all done using a frequency range of

0.05–100 Hz, using the diagnostic mode. Hence, we believe that it is valid to compare the values of ST-segment change in the patients in our study with the other ischemia detection devices.

Transesophageal Echocardiography Versus Printed Electrocardiography (Ischemia Defined by ST Segments or T Waves, or Both)

When data were examined for all periods during the operative procedures, we found that TEE and analysis of the ST segments of printed ECGs had the capacity to detect myocardial ischemia similar to previous series of high-risk patients undergoing noncardiac surgery. When TEE was taken as the reference standard, the sensitivity of the printed ECG was only 25% for ST-segment changes and 40% for ST-segment changes or T-wave inversions, or both. Smith et al. (23) reported that during aortic and coronary bypass surgery, TEE detected intraoperative myocardial ischemia in four times as many patients as did printed ECG, with ST-segment depression used as a criteria. We found that the addition of T-wave criteria for the detection of myocardial ischemia using the printed ECG increases the sensitivity of the printed ECG from 25% to 40% compared with the reference TEE. We had decided prospectively to examine the usefulness of adding T-wave inversions in the definition of myocardial ischemia. We did this because previous studies had shown a low sensitivity for ischemia detection by ST-segment change compared with TEE. We hypothesized that the addition of the T-wave criteria might enhance capacity to detect myocardial ischemia. Supporting this hypothesis is a study of patients with resting T-wave inversions who underwent exercise radionucleotide angiography stress testing (24). A significantly higher incidence (62% vs 28%) of new wall motion abnormalities was noted in patients in whom new T-wave inversions occurred compared with those without new T-wave inversion (24). T-wave changes were more sensitive, although less specific, than were ST-segment changes seen with stress ECG.

In reviewing data comparing mechanical, electrocardiographic, metabolic, and hemodynamic indicators of myocardial ischemia in patients with coronary artery disease undergoing vascular surgery, Haggmark et al. (1) suggested the possibility that "accepted criteria (ST segment changes only) for interpreting the ECG to indicate myocardial ischemia during anesthesia are too stringent." Our data concerning the association of T-wave changes with TEE ischemia might seem to confirm this, because three of four patients with isolated T-wave changes also developed new SWMA; however, the number of such patients was very small. Other workers have suggested that T-wave changes are benign. Breslow et al. (25) concluded that T-wave inversions in the recovery room did not predict perioperative morbidity and mortality. However, the patient population in that study had a low "pretest probability" of having coronary artery disease. Our data, which show that three of the four patients with T-wave inversions in the absence of ST-segment changes had wall motion abnormalities, lead us to conclude that T-wave changes in a high-risk population may be associated with an ischemic TEE examination. However, we do not know whether either T-wave inversions or SWMAs were associated with adverse outcome in this study. The T-wave changes or SWMAs, or both, may be such sensitive indicators of myocardial ischemia that they may have a low predictive value for cardiac complications. Indeed, London et al. (12) showed that SWMAs were only associated with a 6% incidence of cardiac complications.

Automated ST-segment analysis devices are probably better than the "naked eye" in detecting ischemia, but they may be misleading. Because its positive predictive value is only 36% for the MQ system and 35% for the HP system as detected by our reference standard of TEE, each episode of ST-segment sum change of 1 mm or greater represents only approximately a one-third chance that the patients will be found to have myocardial ischemia by TEE. Our view, however, is that an ST-segment trend monitor should be considered an alarm that causes the clinician to increase vigilance. Thus, although our data do not prove our hypothesis that ST-segment trend analysis detects the same incidence of intraoperative myocardial ischemia as does printed multilead ECG or TEE, the two ST-segment trend monitors evaluated may prove useful to indicate the need for the anesthesiologist to examine the patients' ECG carefully. The indicators are useful because intraoperative ischemic episodes tend to be brief and therefore unrecognized by clinicians (12). Brief intraoperative ischemic episodes may herald longer postoperative episodes. If this were true, recognition of intraoperative ischemia may identify patients who might benefit from aggressive postoperative antianginal therapy; however, this is a hypothesis that remains unproved.

Further studies are needed to provide the clinician with reliable, inexpensive, and simple monitors for detecting intraoperative myocardial ischemia. In high-risk patients, ST-segment trend monitors may be used as an alarm, in conjunction with the review of printed ECG strips during surgery, potentially improving the detection of myocardial ischemia. However, these ECG modalities may not predict the presence of wall motion and thickening changes as seen in TEE. Further study is necessary to determine which intraoperative monitoring devices are best for predicting patient outcome.

The lack of concordance of monitors of intraoperative myocardial ischemia leaves us unable to define a reference standard for its detection. The myocardial ischemia detected in this study was often not severe, which may explain the discordance of the different modalities and the relatively low intraobserver variability of TEE readings. The use of more stringent criteria may be needed to predict adverse patient outcome. However, because our study did not follow patients to determine the incidence of postoperative cardiac complications, we cannot compare the capacity of the different intraoperative monitors to predict adverse events. Both TEE and printed ECG appear from other studies to have low positive predictive values for postoperative complications. Changes in either monitor probably need to be severe and long-lasting to predict adverse outcome. The recent demonstration that postoperative myocardial ischemia occurs more frequently than intraoperative or preoperative ischemia (4) suggests that the capacity to diagnose intraoperative myocardial ischemia may be of limited value in predicting patient outcome.

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Lung Traction Causes an Increase in Plasma Prostacyclin Concentration and Decrease in Mean Arterial Blood Pressure

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The effects of lung traction on arterial blood pressure and plasma prostacyclin concentrations were studied in five patients undergoing partial pneumonectomy or lobectomy. After manual traction of a lung segment, mean arterial blood pressure decreased from 77 ± 5 mm Hg (mean ± SEM, before lung traction) to 59 ± 5 mm Hg. The concentrations of 6-keto prostaglandin $F_{1\alpha}$ (a stable breakdown product of prostacyclin) increased significantly from 46 ± 6 pg/mL (mean ± SEM, before thoracotomy) to 593 ± 91 pg/mL. Four of five patients showed facial flushing and palmar erythema. Arterial blood pressure returned to pretraction value, and both the facial flushing and palmar erythema disappeared within 30 min after lung traction. These results suggest that traction of the lung stimulates release and/or production of prostacyclin, which results in facial flushing, palmar erythema, and decrease in arterial blood pressure.

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Prostacyclin (PGI_2), a potent vasodilator, is released after mesenteric traction in aortic surgery (1–3) and after closure of the peritoneum during cesarean section (4). In those situations, arterial blood pressure may decrease in association with facial flushing (1–4).

Prostacyclin is generated in the vascular wall (5,6). Distention of the vessel is thought to stimulate the release of PGI_2 (7). Recently, we observed a decrease in arterial blood pressure after lung traction during pneumonectomy. The patient showed facial flushing and palmar erythema that were similar to what we observed in a previous study in which we demonstrated the release of PGI_2 during cesarean section (4). Mechanical manipulation of the lung (8) or hyperventilation (7) causes release of PGI_2, which may affect the pulmonary circulation. It is well-known that systemic administration of PGI_2 decreases arterial blood pressure; however, it is not known whether PGI_2 released from the lung causes decreased arterial blood pressure. The purpose of this study was to determine whether the decrease in arterial blood pressure after lung traction is associated with an increased plasma concentration of PGI_2.

Methods

After receiving institutional approval, five (male and female) patients, ASA physical status I or II, aged 14–71 yr, who were undergoing partial pneumonectomy or lobectomy because of pneumothorax or lung cancer, were studied. Informed consent was obtained from each patient. Patients had no history of cardiovascular disease. All patients received atropine (0.5 mg IM) and hydroxidine (50 mg IM) 30 min before induction of anesthesia. For postoperative pain management, an epidural catheter was inserted in all patients. Except for a test dose of 2 mL of 2% lidocaine, no additional lidocaine was administered during the study period. Anesthesia was induced with thiopental (4 mg/kg IV), followed by vecuronium (0.08 mg/kg) to facilitate endotracheal intubation. A radial artery was cannulated for the measurement of arterial blood pressure and sampling of blood. Anesthesia was maintained with enflurane (1%–2%) and nitrous oxide (60%–66%) in oxygen. The concentration of enflurane was maintained as constant as possible during the study period. After thoracotomy, the lung segment to be resected was grasped in the surgeon's hands, and manual traction

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Table 1. Changes in Mean Arterial Pressure and Heart Rate in Five Patients Undergoing Partial Pneumonectomy or Lobectomy

Pt No./ Gender	Mean arterial pressure (mm Hg)			Heart rate (beats/min)		
	Before traction	5 Min after traction	30 Min after traction	Before traction	5 Min after traction	30 Min after traction
1/M	87	67	88	85	109	83
2/M	73	45	82	80	75	70
3/M	63	56	82	52	52	60
4/F	87	73	83	90	90	75
5/M	77	55	83	78	78	82
Mean ± SEM	77 ± 5	59 ± 5[a]	84 ± 1	77 ± 7	81 ± 9	74 ± 4

Pt, patient.
[a] $P < 0.05$, significantly different from baseline.

was applied for 30 s. This traction was performed in a standardized fashion by the same surgeon in all five patients.

Mean arterial pressure (MAP) and heart rate (HR) were measured before traction and 5 and 30 min after traction. Blood samples for prostanoid analysis were collected before thoracotomy and 5 and 30 min after traction. To avoid artifactual release of prostanoids, the blood samples were slowly withdrawn into disposable plastic syringes and transferred into ice-chilled plastic tubes containing ethylenediaminetetraacetate (1 mg/1 mL blood) and indomethacin (0.036 mg/1 mL blood). The blood samples were placed on ice immediately and centrifuged at 4°C. After centrifugation, plasma was frozen and stored at −80°C. The concentrations of plasma 6-keto prostaglandin $F_{1\alpha}$ (6-keto $PGF_{1\alpha}$), a stable breakdown product of PGI_2, and thromboxane B_2 (TXB_2), a stable breakdown product of thromboxane A_2, were measured by the radioimmunoassay method. Radioimmunoassay for 6-keto $PGF_{1\alpha}$ was performed on the incubation mixture, which consisted of 0.8 mL of sample or standard (Ono Pharmaceutical Co., Osaka, Japan), 0.1 mL of [^{3}H]6-keto $PGF_{1\alpha}$ (specific activity 130.0 Ci/mmol; New England Nuclear Co., Boston, Mass.), and 0.1 mL of anti-6-keto $PGF_{1\alpha}$ serum (final dilution 1:3000; Advanced Magnetics Co., Cambridge, England). The interassay and intraassay coefficients of variation of 6-keto $PGF_{1\alpha}$ were 8.6% and 10.5%, respectively. Radioimmunoassay of TXB_2 was performed as described for 6-keto $PGF_{1\alpha}$ using standard TXB_2 (Ono Pharmaceutical), [^{3}H]TXB_2 (specific activity 196.8 Ci/mmol; New England Nuclear), and anti-TXB_2 (final dilution 1:16,000; Ono Pharmaceutical). The interassay and intraassay coefficients of variation of TXB_2 were 7.2% and 8.3%, respectively. The detection limit of 6-keto $PGF_{1\alpha}$ and TXB_2 in this method was 20 pg/mL.

Data were statistically analyzed by the Kruskal-Wallis one-way analysis of variance, followed by the Mann-Whitney rank sum test. A value of $P < 0.05$ was considered significant.

Results

Traction of the lung was associated with a significant reduction in MAP (Table 1), and a significant increase in 6-keto $PGF_{1\alpha}$ at 5 min (Table 2) after traction was applied. Facial flushing and palmar erythema were observed in four patients within the 5-min period after lung traction. By 30 min, MAP returned to pretraction values, and both flushing and erythema disappeared. We decreased the concentration of enflurane in one patient (patient 2) until MAP returned to 55 mm Hg because of hypotension after traction. The concentration of 6-keto $PGF_{1\alpha}$ remained elevated compared with prethoracotomy values at 30 min after traction. The concentrations of TXB_2 increased after traction in some patients, but there was no significant difference in the concentration of TXB_2 compared with baseline values in the group as a whole. There was no significant change in HR from baseline at any time (Table 1).

Discussion

In the current study, we demonstrated that traction of the lung is associated with a decrease in MAP and an increased plasma concentration of 6-keto $PGF_{1\alpha}$ (a stable breakdown product of PGI_2). Prostacyclin is continuously generated in the lung and acts as a circulating hormone (5). Endothelial cells lining blood vessels, including the pulmonary vessels, potentially produce PGI_2 (5,6). The production or release of PGI_2 is enhanced after mechanical stimulation, such as distention of the vessels (7). Several investigators have reported that abdominal mesenteric traction decreases MAP and increases HR, which is accompanied by an increased concentration of plasma 6-keto

Table 2. Changes in Concentrations of 6-keto $PGF_{1\alpha}$ and Thromboxane B_2, and Appearance of Facial Flushing in Five Study Patients

	6-keto $PGF_{1\alpha}$ (pg/mL)			Thromboxane B_2 (pg/mL)			
Pt No.	Before thoracotomy	5 Min after traction	30 Min after traction	Before thoracotomy	5 Min after traction	30 Min after traction	Facial flushing
1	31	573	188	99	364	359	+
2	57	666	468	49	82	69	+
3	56	524	405	28	24	77	+
4	32	322	144	57	58	143	−
5	56	879	422	20	62	351	+
Mean ± SEM	46 ± 6	593 ± 91[a]	325 ± 66[a,b]	51 ± 14	118 ± 62	200 ± 65	

[a] $P < 0.01$, significantly different from baseline.
[b] $P < 0.05$, significantly different from the value at 5 min after traction.

$PGF_{1\alpha}$ (1–4). Both lung and mesentery contain vessels that may be distended by traction.

We did not measure plasma concentrations of 6-keto $PGF_{1\alpha}$ or TXB_2 immediately before traction of the lung. It is appropriate to ask whether surgical incision itself may increase the concentration of 6-keto $PGF_{1\alpha}$. Goto et al. (9) reported that laparotomy significantly stimulated the release of PGI_2 under general anesthesia. They showed that the concentration of 6-keto $PGF_{1\alpha}$ significantly increased from <10 to 55 pg/mL 20 min after start of surgery (9). However, there was no comment relating the elevation of 6-keto $PGF_{1\alpha}$ to surgical activity. The peak concentration of 6-keto $PGF_{1\alpha}$ in their study is less than that in ours, and there was an increase rather than a decrease in MAP associated with the increase in the concentration of 6-keto $PGF_{1\alpha}$ (9). In contrast, Seltzer et al. (1) did not find a significant change in the plasma concentration of 6-keto $PGF_{1\alpha}$ after laparotomy under general anesthesia. In our study, there was no flushing or palmar erythema before traction of the lung. Therefore, we think it unlikely that surgical incision itself increased the concentration of PGI_2 to the degree in which apparent vasodilation was observed in our study.

The concentrations of 6-keto $PGF_{1\alpha}$ after pulmonary traction were less than those reported after mesenteric traction (1–4). This may represent a difference in the amount of vascular bed that was involved in the traction or a difference in the intensity of the traction. In the current study, traction was performed as consistently as possible by the same surgeon. The peak concentration of 6-keto $PGF_{1\alpha}$ in one patient (patient 4) was low, and that patient did not show flushing or palmar erythema. The structure of the lung that was retracted in that patient was almost destroyed because of large bullae. It is possible that the manipulated part of the lung may have contained fewer vessels in this patient than in the others. This supports the hypothesis that distention of the vessels stimulates the production and/or the release of PGI_2.

The cyclooxygenase inhibitor ibuprofen (administered orally before anesthesia) has been demonstrated to prevent an increase in the concentration of 6-keto $PGF_{1\alpha}$ and a decrease in arterial blood pressure in the setting of mesenteric traction (1,3). Although cyclooxygenase inhibitors have side effects, such as inhibition of platelet function, they may be useful in preventing the abrupt decrease in arterial blood pressure in the setting of lung traction.

Hudson et al. (3) reported a late increase of TXB_2 after mesenteric traction in abdominal aortic surgery. They suggest that the late increase of TXB_2 represents the regulatory response to elevated PGI_2 synthesis and vasodilation (3). We also measured TXB_2 concentrations but did not find late elevations of TXB_2. In our study, HR did not increase significantly after traction. This may be due to the lesser degree of peak concentration of 6-keto $PGF_{1\alpha}$ that we observed. Also, the number of patients in our study was small. Further studies may be necessary to further elucidate the HR response or TXB_2 response, or both.

In conclusion, we demonstrated that lung traction is associated with an increased plasma concentration of 6-keto $PGF_{1\alpha}$ and a reduction in MAP. Although the hypotension may have been due to a mechanical effect in the lung (i.e., reduced venous return to the heart), PGI_2-induced vasodilation should now be a consideration in the differential diagnosis of this phenomenon.

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Efficacy of Anticholinergic and β-Adrenergic Agonist Treatment of Maximal Cholinergic Bronchospasm in Tracheally Intubated Rabbits

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Cholinergically induced bronchoconstriction is thought to be a major cause of bronchospasm during anesthesia. We used tracheally intubated rabbits (4-mm endotracheal tube) stimulated with methacholine to assess the efficacy of β-adrenergic agonist and anticholinergic treatment in reversing the increases in respiratory system resistance. Four groups were compared: (a) inhaled metaproterenol, 20 puffs via metered dose inhaler (0.65 mg/puff); (b) inhaled ipratropium bromide, 20 puffs from a metered dose inhaler (18 μg/puff); (c) 2 mg of intravenous atropine; and (d) no treatment after methacholine challenge as a control group. Methacholine increased respiratory system resistance from 0.041 ± 0.001 (mean ± SEM) to 0.098 ± 0.006 cm $H_2O \cdot mL^{-1} \cdot s^{-1}$ ($P < 0.001$). Whereas β-adrenergic agonist treatment was ineffective in ameliorating bronchoconstriction, inhaled ipratropium bromide and atropine were highly effective, causing an 86%–88% reversal in the methacholine-induced increase in respiratory system resistance. Both these agents were also effective in improving dynamic compliance. We conclude that inhaled ipratropium bromide is effective in treating cholinergic bronchospasm even when administered via a small endotracheal tube and that the β-adrenergic agonist metaproterenol is ineffective in rabbits in the face of maximal cholinergic stimulation.

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During tracheal intubation and anesthesia, mechanical stimulation of receptors in the nose, larynx (1), or airways (2) may precipitate vagally mediated reflex bronchoconstriction and mucus secretion (3,4). The usual treatment of intraoperative bronchospasm includes deepening of anesthesia (5,6) and administration of a β-adrenergic agonist (7). Inhaled anesthetics attenuate pulmonary bronchoconstriction by blocking vagal reflexes and by direct smooth muscle relaxation (8–10); β-adrenergic agonists relieve bronchospasm by stimulating β-adrenergic receptors and inducing smooth muscle relaxation (11).

In the proposed study, we assessed the efficacy of inhaled bronchodilator treatment of methacholine-mediated bronchospasm using a rabbit model in which the trachea was intubated with a 4.0-mm inner diameter endotracheal tube (ETT). We produced maximal bronchoconstriction with methacholine and then compared treatments with the β-adrenergic agonist metaproterenol, inhaled ipratropium bromide (IB), or parenteral atropine. We attempted to answer the following questions: (a) Are inhaled bronchodilator agents effective when delivered via an ETT using a metered dose inhaler (MDI)? (b) How effective is inhaled anticholinergic therapy compared with parenteral therapy?

Methods

We performed a total of 28 studies in seven adult New Zealand White rabbits with a mean weight of 3.2 ± 0.1 kg (mean ± SEM) (range 2.7–4). Animals were anesthetized with pentobarbital sodium (30 mg/kg IV) and intubated orally with a 4.0-mm cuffed ETT. Each rabbit was then paralyzed with pancuronium bromide (0.3 mg IV) and ventilated with 100% oxygen by a piston-type ventilator (Harvard Apparatus, Millis, Mass.) set to deliver a tidal

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volume of 15 mL/kg at a frequency of 25 breaths/min (Ttot = 2.4 s) and an inspiratory cycle of 0.33 (Ti = 0.8 s). The electrocardiogram was monitored, and anesthesia was maintained by an intravenous bolus dose of 20% of the initial dose of sodium pentobarbital and 0.1 mg of pancuronium every hour.

Tracheal flow was measured through a heated pneumotachograph head (Hewlett Packard, Waltham, Mass.) and a differential flow transducer (Hewlett Packard model 47303A) placed between the Y-piece of the ventilator circuit and the ETT tube. Flow signals were calibrated by timed volume accumulation in a 9-L respirometer. Airway pressure was measured at the mouth side of the pneumotachograph. All signals were amplified, filtered, and recorded by a 12-bit analogue-to-digital converter, sampled at a rate of 100 Hz, and stored on an IBM/AT compatible computer.

Dynamic compliance (Cdyn) of the respiratory system was calculated as tidal volume divided by change of airway pressure measured at the two points of zero flow. Respiratory system resistance (Rrs) was calculated using the isovolume technique (12) at a lung volume of 30 mL above functional residual capacity. Five minutes before each measurement, the trachea was suctioned, and three total lung capacity inflations (peak airway pressure 35 cm H_2O) were performed to standardize volume history.

During 11 separate studies in five of the rabbits, we also inserted a fluid-filled catheter to the point in the esophagus where end-expiratory pressure was minimal. During this series, we measured lung resistance (Rl) from transpulmonary pressures (airway minus esophageal pressure) at the isovolume points. We then confirmed that Rrs correlated closely with Rl in our anesthetized, paralyzed rabbits (Figure 1).

A dose-response curve to methacholine was obtained in three rabbits to determine the concentration of methacholine that assured maximal bronchomotor response. Each rabbit was challenged with normal saline solution and then increasing concentrations of methacholine (1.6–100 mg/mL in doubling concentrations) for 3 min at 20-min intervals. The medications were delivered as an aerosol generated by an ultrasonic nebulizer (Ultra-Neb, model 099HD, DeVilbiss) in line with the ventilator circuit. The "dose" of methacholine deposited on the airways is actually not known. Nevertheless, as ventilatory variables were uniform, the dose should be proportional to the concentration of active agent. Fifteen minutes after each challenge, pulmonary mechanics data were recorded and Rrs calculated. In all three rabbits, Rrs demonstrated a plateau at 25–50 mg/mL (change in Rrs of <20% after a response of >200% over baseline). Severe dysrhythmias but no increase in bronchoconstriction were noted when concentrations of 100 mg/mL of methacholine were used. Our finding that 50 mg/mL provided maximal response confirmed the data of Romero and Ludwig (13), who noted peak response at a concentration of methacholine between 32 and 64 mg/mL. Accordingly, we used 50 mg/mL of methacholine to obtain a plateau response for subsequent studies.

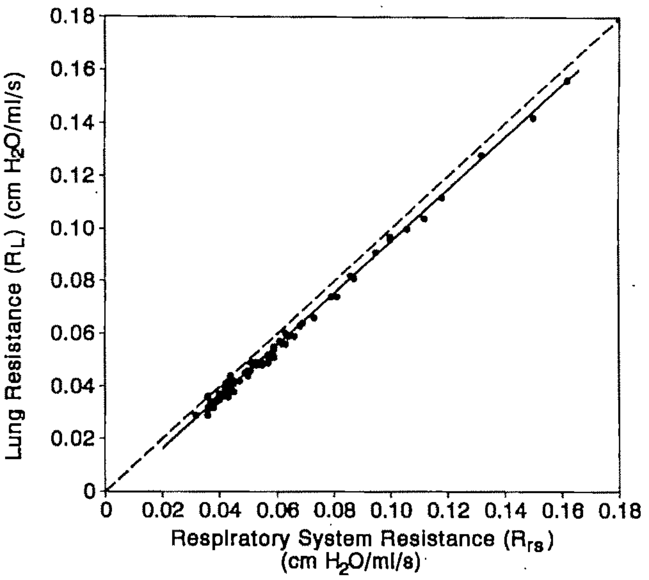

Figure 1. Correlation of Rl with Rrs: $r = 0.998$; $P < 0.001$; $n = 11$, Rl = 0.986 (Rrs) − 0.004. *Dashed line* is the line of identity. The constant of 0.004 for the difference between Rl and Rrs represents chest wall resistance.

After two baseline values of Rrs and Cdyn had been obtained 2 min apart, the rabbits were challenged with 3 min of 50 mg/mL of inhaled methacholine generated by the ultrasonic nebulizer. Pulmonary mechanics were recorded again at 15, 35, 55, and 75 min after commencing the challenge. Each rabbit received four different treatment regimens performed in random order 1–3 days apart. The treatment regimens were begun after the 15-min post-methacholine data collection point. The four treatments included

1. Inhaled metaproterenol, 20 puffs via MDI (0.65 mg/puff)
2. Inhaled ipratropium bromide (IB), as a single dose of 20 puffs via MDI (18 μg/puff)
3. Single dose of atropine (2 mg IV) administered at 30 min after methacholine challenge
4. No treatment as a control group

The MDI treatments were performed using at least five different inhalers per treatment to minimize any effect of variability among inhalers. Each MDI was shaken vigorously before use. Each puff of MDI was delivered with a 5-s inflation to an inspiratory pressure of 35 cm H_2O.

All treatment groups other than group 3 (IV atropine) received a single dose of atropine (2 mg IV) after data collection at the 75-min point to document that reversible bronchoconstriction still persisted. Pulmonary mechanics were measured 10 min later to record the efficacy of the atropine treatment. Treatment efficacy was assessed as a percent reversal of the response to methacholine. Thus,

$$\%\text{ Rrs reversal} = \frac{\text{Rrs(MC)} - \text{Rrs(Treatment)}}{\text{Rrs(MC)} - \text{Rs(Baseline)}} \times 100,$$

$$\%\text{Cdyn reversal} = \frac{\text{Cdyn(Treatment)} - \text{Cdyn(MC)}}{\text{Cdyn(Baseline)} - \text{Cdyn(MC)}} \times 100,$$

where Rrs(MC) and Cdyn(MC) represent Rrs and Cdyn, respectively, at 15 min after methacholine; Rrs(Baseline) and Cdyn(Baseline) represent the average value of the two sets of baseline data, and Rrs(Treatment) and Cdyn(Treatment) represent the values for subsequent treatments. Thus, a value of 0 would represent no improvement after treatment, and a value of 100 would represent a return to the baseline value.

Data were analyzed using one-way analysis of variance to determine the significance between group differences, followed by least-significant difference testing to determine differences between the control (methacholine alone) group and the various treatments (14).

Results

Methacholine inhalation more than doubled Rrs within 15 min from a mean of 0.041 ± 0.001 to a mean of 0.098 ± 0.006 cm $H_2O \cdot mL^{-1} \cdot s^{-1}$ ($P < 0.001$).

In the 11 studies in which we measured RL separately, we found that the effect of methacholine on chest wall resistance, Rcw = (Rrs − RL), was minimal. Although Rcw increased from a mean of 0.004 ± 0.001 to 0.006 ± 0.001 after methacholine, this effect was small compared with the overall increase in resistance (3.5% of the increase).

Significant reversal of the elevation in Rrs occurred only after treatment with inhaled IB or intravenous atropine (Figure 2). Reversal with IB was 86% ± 3% at 35 min after methacholine challenge and further increased to 96% ± 2% at 55 min after methacholine challenge. Atropine reversal was 88% ± 7% initially but then declined to 76% ± 12% at 55 min. In the absence of any treatment, spontaneous reversal of the increase in Rrs was 30% ± 4% at 35 min and 34% ± 5% at 55 min. Metaproterenol was not effective compared with the spontaneous reversal.

Methacholine decreased Cdyn of the respiratory system approximately 30% from a mean of 3.15 ± 0.07 to a mean of 2.19 ± 0.04 mL/cm H_2O ($P < 0.001$) at a respiratory rate of 25 breaths/min. Spontaneous reversal of this decrease in the untreated group was prolonged: 33% ± 8% at 35 min after challenge and 55% ± 7% at 55 min after challenge. Both atropine and IB were successful in substantially and rapidly reversing the initial decline in Cdyn, although only atropine had a persistent beneficial effect that was clearly different from the spontaneous improvement (Figure 3).

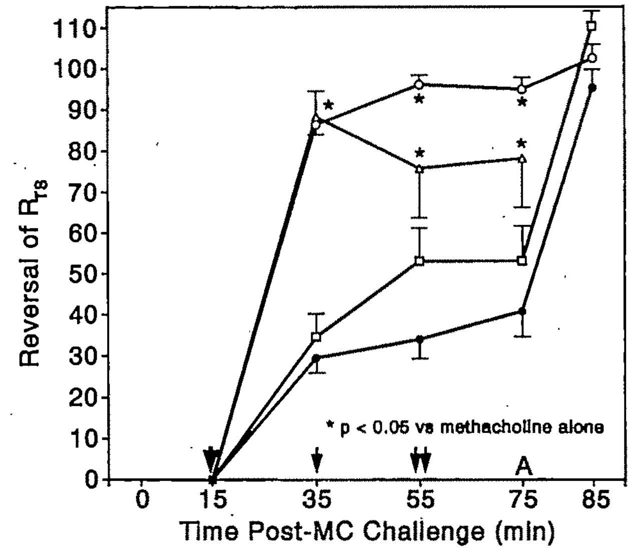

Figure 2. Percentage reversal in respiratory system resistance (Rrs) after treatment with anticholinergic and β-adrenergic agonists. The Rrs was raised approximately 150% above baseline by methacholine (MC) at t = 0. *Large arrow* is the time point of initial treatment at 15 min. No significant differences are noted between the β-adrenergic agonist and the untreated controls. ●——●, MC alone, no treatment; ○——○, IB, ipratropium bromide; □——□, MDI 20, single-dose 20 puffs of metaproterenol. △——△, atropine (2 mg IV) administered at 75 min, indicated by *A*, to all except the atropine group. Data are mean ± SE.

At the conclusion of this study, atropine (2 mg IV) significantly decreased resistance to within 15% of baseline in all groups (other than the original intravenous atropine group, which did not receive further atropine) (Figure 2). However, atropine administration did not lead to significant further improvement in Cdyn (Figure 3).

Methacholine significantly decreased heart rate both during the 3-min challenge and 5 min after the challenge (Figure 4). At 15 min after methacholine, heart rate recovered spontaneously in the control group and stabilized during the rest of the experiment. Heart rate for all treatment groups did not differ significantly from the control group. Intravenous atropine administered at the conclusion of the study had no additional effect on heart rate.

Discussion

In this study we compared the effectiveness of various strategies for reversing cholinergic bronchocon-

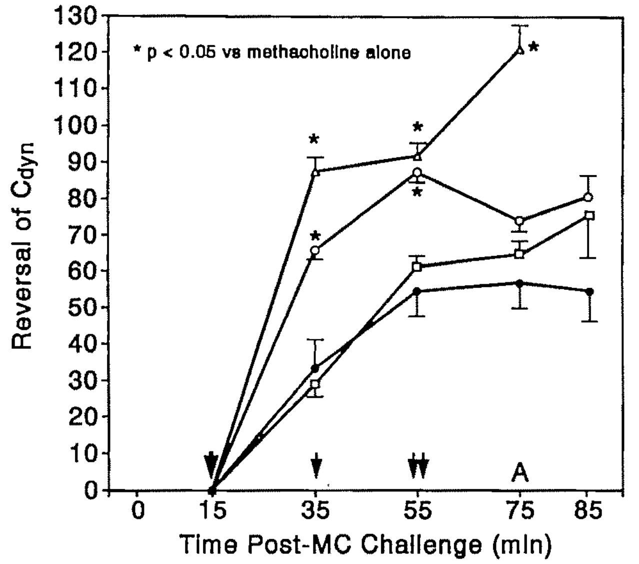

Figure 3. Percentage reversal of the methacholine (MC)-induced increase in Cdyn after treatment with anticholinergic and metaproterenol. *Large arrow* was time point of initial treatment. Abbreviations and symbols as in Figure 2.

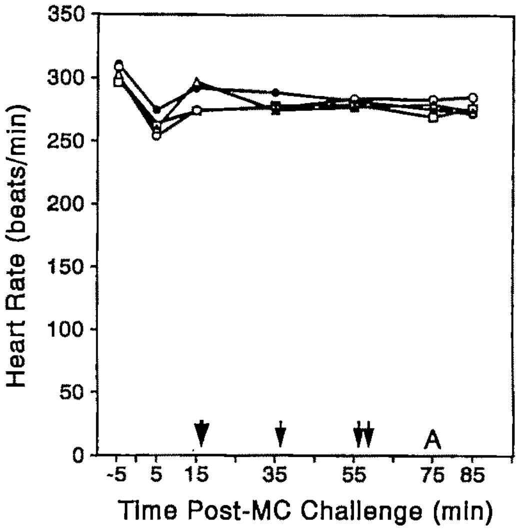

Figure 4. Mean heart rate after methacholine (MC) challenge and treatment with anticholinergic or β-adrenergic agent. Intravenous atropine (2 mg) was administered at 75 min, indicated by *A*. Pulse rate decreased significantly after methacholine challenge ($P < 0.001$). No significant differences were noted among the regimens. Standard errors were omitted for clarity in this figure. Abbreviations and symbols as in Figure 2.

striction modeled by aerosol administration of methacholine to anesthetized, paralyzed rabbits. The important findings of this study are the following:

(a) Aerosol from an MDI can provide effective treatment via a small ETT, as demonstrated by the efficacy of IB.
(b) β-Agonist treatment of a maximal methacholine stimulus was not effective in this model.
(c) Inhaled anticholinergic therapy with IB provides therapeutic efficacy equal to that provided by complete parenteral parasympathetic blockade with atropine.

After tracheal intubation, only 2%–10% of the drug from an MDI reaches the airway, even if the proper technique is used (15). This amount may be even less in pediatric-sized ETTs such as those used in this study. We therefore tested an initial dose of 20 puffs of the metaproterenol to ensure that an adequate dose was delivered to the airways in order to compare the efficacy of the drugs.

The IB and metaproterenol were administered using identical delivery systems that produce a similar profile of droplet size. A significant portion of the droplets are in the appropriate range for airway deposition (1–5 μm) (16). Penetration of the aerosols into the lungs should therefore have been identical.

We chose IB as an inhaled drug to study its efficacy against a maximal cholinergically induced bronchial response, because it is a direct cholinergic antagonist and thus relieves bronchospasm via a mechanism different from the β-adrenergic agonist (17). We used parenteral atropine in a large dose as a positive control. The dose of atropine used was based on the uniform and complete reversal of methacholine bronchospasm previously reported by Romero and Ludwig (13). Metaproterenol is an effective β-adrenergic agonist in the treatment of obstructive lung disease (18,19) when used in doses far lower than those used in our study. The dose we used was approximately 200 times the usual per kilogram dose in adult humans.

The dose of IB chosen was high relative to human doses, raising the possibility that its effect was achieved by systemic absorption. However, unlike atropine, which undergoes complete and rapid absorption from the mucosa, IB is <1% absorbed and is thus unlikely to have been effective because of systemic absorption (17).

Rabbits were studied multiple times in a randomized order to control for the effects of repeated intubation and methacholine challenge. We chose a rabbit model because of the rabbits' relatively uniform bronchoconstrictive response to methacholine without airway hyperreactivity (13). Great caution must be taken in extrapolating our results to humans. These results are not intended to be a model of reactive airways disease but may reflect the effects seen with reflex cholinergic bronchoconstriction, a phenomenon thought to be responsible for some cases of intraoperative bronchospasm. The specific questions we addressed with regard to drug delivery cannot be answered for humans with absolute certainty other than in a human model. Although the rabbit provides a reliable model of cholinergic-induced increased airway resistance, there are differences between this model and human intraoperative bronchospasm.

Many cases of intraoperative bronchospasm involve patients with underlying obstructive lung disease and reactive airways. However, in a review of 14 consecutive cases of intraoperative bronchospasm at one author's institution, 50% of the patients had no history, signs, or symptoms of underlying reactive airways disease, and cholinergic reflexes have been hypothesized to be an underlying mechanism of such bronchospasm (20). Thus, we believe that there is validity in using cholinergic bronchospasm as a model.

We studied a maximal dose of methacholine. It is unknown whether in humans such a maximal cholinergic stimulus ever occurs. Hence, we are really studying a worst-case scenario. Additionally, even in reflex bronchospasm, a variety of other mediators may be released. Thus, our model must be viewed as having many differences from the clinical situation, and our conclusions must be viewed more as indications for further studies.

Rrs rather than RL was used to study the response because of its simplicity of measurement, requiring only airway pressure and flow data. Furthermore, technical difficulties due to esophageal secretions and catheter movement leading to artifacts can make measurements of RL less reproducible. Nevertheless, we documented close correlation between the two measurements in our totally paralyzed rabbits (Figure 1).

The measured changes in Rrs reflect a combination of changes in chest wall resistance (Rcw), airway resistance, and lung tissue viscosity (13). These components can be differentiated only by direct measurements of alveolar pressure. The Rcw changes were minimized by the use of neuromuscular paralysis. Mean Rcw was 0.004 cm $H_2O \cdot mL^{-1} \cdot s^{-1}$, or approximately 20% of Rrs exclusive of the ETT and did not change after methacholine administration. The overall effect on pulmonary mechanics does not differ whether changes in Rrs are due to changes in airway resistance or lung viscosity. It is of no consequence to the management of the clinical problem of increased Rrs to differentiate the source of the increase.

Our mean measured control Rrs of 0.041 cm $H_2O \cdot mL^{-1} \cdot s^{-1}$, when corrected for the resistance of the ETT, which we determined to be 0.020 cm $H_2O \cdot mL^{-1} \cdot s^{-1}$ at the flow rates used, corresponds closely to previously measured values in rabbits of 0.020 cm $H_2O \cdot mL^{-1} \cdot s^{-1}$ (13).

The β-adrenergic agonists reverse bronchoconstriction caused by a cholinergic stimulus (21). Cholinergic agonists induce increased tone by binding to smooth muscle cell surface receptors that operate via stimulatory G-proteins (Gs) and ultimately result in Ca^{2+} release from endoplasmic reticulum, resulting in muscle contraction. In addition, they can inhibit adenylate cyclase. β-Adrenergic agonists are thought to relax smooth muscle by binding to a different cell surface receptor and, via an inhibitory G-protein (Gi), increase adenylate cyclase activity and, ultimately, cyclic adenosine monophosphate, a smooth-muscle relaxant (22). Thus, β-adrenergic agonists should partially interfere with cholinergically induced spasm. Cholinergic antagonists act as direct competitors for the cholinergic receptor site.

Previous studies demonstrating the efficacy of β-adrenergic agonists in cholinergic bronchoconstriction have differed from ours in not assessing a maximal stimulus. Our results agree with another study that noted that bronchodilator potency of β-adrenergic agonists is reduced during marked bronchoconstriction, such as occurs in severe asthma or with the experimental administration of high doses of a constrictor agonist (23). We conclude that even though β-adrenergic agonists play a major role in relieving bronchoconstriction in a variety of circumstances, conventionally used doses may not reverse maximal cholinergic challenge. Although much larger doses might be effective, existing dose-response curves for β-adrenergic agonists suggest that most of their effects should occur at the concentrations we delivered. Thus, metaproterenol conceivably could shift the dose-response curve but did not prove effective at the maximal methacholine response.

Ipratropium bromide was as effective as atropine in treating the increase in Rrs at the first time point and had a more persistent effect. Intravenous atropine had a peak effect at the first time point, but then declined in efficacy, probably due to its short duration of action.

Reversal of Cdyn was significant in both the atropine and IB groups compared with the control and β-adrenergic agonist groups at the first point after treatment (35 min). However, as spontaneous recovery of compliance increased, inhaled IB failed to demonstrate any significant difference from the other groups, whereas the effect of intravenous atropine persisted. Because Cdyn is a function of more peripheral small airways, this difference may be explained by the differences in route of administration of the drugs. Previous studies in normal subjects have shown a greater bronchodilator effect in large central airways than in peripheral airways after inhaled but not intravenous atropine (24,25). This remains controversial, and other studies have failed to localize any degree of preferential bronchodilatory effect of the IB in normal subjects (26) or in patients with asthma (27). Inhaled IB is primarily deposited in larger airways and might theoretically produce greater bronchodilation in larger airways where it is best delivered. Changes in Rrs primarily reflect changes in more central airways, whereas changes in Cdyn typically reflect changes in the more peripheral airways. Thus, efficacy of the inhaled drug in reversing Cdyn might be less than the efficacy of a parenteral drug.

Reversible bronchoconstriction still existed at 75 min after methacholine administration, as demonstrated when atropine (2 mg IV) was given. The Rrs in all groups improved to within 15% of the original baseline value after atropine administration.

The trend in heart rate changes was not significantly different in treatment groups compared with the methacholine-only group. Neither atropine nor metaproterenol elicited an increase in heart rate, although a reversal of increased Rrs was noted. The lack of response of heart rate agrees with the observation by Holtzman et al. (28) in dogs; they noted that despite effective inhibition of muscarinic receptors in the airways by anticholinergic agents, response of cardiac muscarinic receptors was unchanged even at the highest dose of atropine. This differs from humans in whom cardiac muscarinic response is seen at doses of atropine required to produce bronchodilation (29). The relative safety of intravenous atropine in rabbits should not necessarily be extrapolated to humans.

One of the purposes of our study was to demonstrate the efficacy of drug delivery using an MDI via an ETT. Previous studies showed that 2%–10% of the weight of a puff from an MDI exits the end of the ETT, but no determination has been made as to whether the drug itself traversed the tube or whether carrier substances in the MDI solution were preferentially preserved at the exit. The response to IB demonstrated that drugs delivered using MDI technology can reach highly effective concentrations in the airways, even with a pediatric-sized ETT in place.

Our studies confirm that inhaled anticholinergic treatment is equally efficacious as total parenteral parasympathetic blockade in this rabbit model. Any extrapolation to the clinical situation must be made with great caution. Reflex bronchoconstriction in humans has a significant cholinergic component but also involves other locally released mediators. Clinical experience has also shown that β-adrenergic agonists are effective in the clinical care of irritant-induced spasm, and β-adrenergic agonists have been shown to be more effective in histamine-induced bronchospasm than in cholinergically induced spasm. Methacholine administration also differs from reflex vagal bronchoconstriction in reversability by β-adrenergic agonists in vitro (30). This may be due to prejunctional effects of the β-adrenergic agonist, which would not play a role during direct application of a cholinergic stimulus. Perhaps the only direct clinical conclusion to be drawn at this point is that addition of inhaled IB to the conventional treatments of bronchospasm during anesthesia might be useful. Given the lack of any toxicity of IB, such a trial seems reasonable.

In conclusion, this study demonstrates that (a) under maximal cholinergic stimulus in rabbits as a model of bronchospasm, both inhaled IB and intravenous atropine relieve bronchoconstriction; (b) the β-adrenergic agonist metaproterenol is ineffective in reversing bronchoconstriction in this model; and (c) effective aerosol doses of a drug (IB) do reach the airways when administered via a 4.0 ETT.

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Comparison of Two Techniques to Inflate the Bronchial Cuff of the Univent Tube

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The Univent tube is an endotracheal tube with a movable bronchial blocker. The blocker cuff reportedly exhibits high-pressure characteristics when inflated to seal any adult bronchus. This study was aimed at measuring the cuff volume that would seal the bronchus when two different techniques of cuff inflation were used. One technique is based on creating negative pressure and the other is based on creating positive pressure within the breathing system. In addition, we directly measured the compliance characteristics of the cuff. The study was performed in eight adult patients undergoing thoracotomy. The negative pressure technique of cuff inflation (NPT) was tested by applying −150 mm Hg of pressure to the blocker lumen, causing loss of volume in the breathing system as evidenced by deflation of the reservoir bag. The blocker cuff was then inflated until the bag ceased to deflate. In the positive pressure technique of cuff inflation (PPT), the blocker lumen was connected to a beaker of water while maintaining pressure of +30 mm Hg within the breathing system. The bronchial cuff was then inflated until air bubbles ceased to appear in the beaker. Direct measurement of compliance of the blocker cuff confirmed its high-pressure characteristics. Bronchial sealing volume ranged from 3 to 5 mL when measured with the NPT and from 4 to 6 mL when measured with the PPT. In most cases, the NPT could provide satisfactory lung collapse with equal or smaller cuff volume than that measured with the PPT, but the smaller cuff volume was associated with only a relatively small reduction in cuff pressure. The PPT provided more reliable bronchial seal against a known airway pressure. It should therefore provide better lung protection in the presence of bleeding or infection.

(Anesth Analg 1992;75:784–7)

The Univent tube is an endotracheal tube with a movable bronchial blocker that is available for one-lung ventilation (1). The blocker cuff exhibits high-pressure characteristics when inflated to seal any adult bronchus (2). It is important, therefore, to inflate the blocker cuff to the smallest volume that would seal the bronchus rather than use 6–7 mL of air to routinely inflate it, as recommended by the manufacturer (Univent; Fuji Systems Corporation, Tokyo, Japan).

Two techniques have been described for inflating the blocker cuff to the bronchial sealing volume. One is based on creating negative pressure within the breathing system (2). The other technique pressurizes the proximal airway to a certain level and then demonstrates that no air leaks from the endobronchial catheter, similar to the procedure used for a double-lumen tube (3). The purpose of this study was to measure the blocker sealing volume using the negative pressure technique (NPT) of cuff inflation and to compare it with the cuff volume that would produce bronchial seal using the positive pressure technique (PPT) of cuff inflation. Because previous description of the high-pressure characteristics of the blocker cuff was based only on measurement of its resting volume and diameter, this study also aimed at directly measuring the pressure-volume relationship of the cuff to document its compliance characteristics.

Methods

The study was approved by the Georgetown University Hospital Institutional Review Board. Eight adult patients undergoing thoracotomy were studied after giving informed consent. Patient characteristics are summarized in Table 1. After induction of general anesthesia, the Univent tube was placed in the trachea. Tubes with an internal diameter of 7 or 8 mm were used, depending on the patient's build. The size of the bronchial blocker is equal in both these tube sizes. After the trachea was intubated, the tube was

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Table 1. Clinical Characteristics of Eight Patients Undergoing Thoracotomy

Age (yr)	64 ± 14
Male/female	4/4
Weight (kg)	80 ± 15
Height (cm)	179 ± 11
Side of thoracotomy (right/left)	4/4

Values are number of patients or mean ± SD.

rotated 90° to the side to be occluded, and the blocker was advanced into the corresponding mainstem bronchus. Fiberoptic bronchoscopy was used to guide the depth of insertion of the blocker, which was placed so that its cuff lay completely within the bronchus just beyond the carina. General anesthesia was maintained with high-dose fentanyl or sufentanil supplemented with 0.5%–1.5% isoflurane in oxygen. Arterial oxygen saturation was monitored continuously with a pulse oximeter.

Compliance of the blocker cuff was first studied. A three-way stopcock connected the inflating tube of the blocker cuff with a 3-mL syringe and a calibrated aneroid manometer. The cuff was inflated with air in 1-mL increments to a total volume of 7 mL. The manometer recorded the cuff pressure that corresponded to each cuff volume. This part of the study was performed in four patients only.

The cuff was then deflated, and the bronchial sealing volume, as measured by NPT, was tested (Figure 1). After the patient's lungs were ventilated several times with 100% oxygen, ventilation was discontinued, the overflow valve in the breathing system was opened fully, and fresh gas flow to the system was turned off. Oxygen was flushed into the system until the reservoir bag became distended. Suction pressure of −150 mm Hg was then applied to the blocker lumen with a 10F suction catheter. With the bronchial cuff deflated, the distal end of the lumen of the blocker was freely connected with the trachea, causing loss of volume in the breathing system, as evidenced by deflation of the reservoir bag. The blocker cuff was then inflated with air in 1-mL increments, and the reservoir bag was observed carefully until it ceased to deflate. This was considered an indication that sealing of the bronchus had been accomplished, and the corresponding cuff volume was recorded. If the reservoir bag was emptied before completion of the test, it was refilled by flushing more oxygen into the breathing system.

Bronchial seal at this point was tested with the PPT. The 10F suction catheter now connected the blocker lumen to a beaker of water (Figure 2). The breathing system attached to the Univent tube was pressurized to +30 mm Hg. Complete seal at that pressure was confirmed if no air bubbles appeared in the beaker. Incomplete seal, on the other hand, led the pressurized air to escape through the blocker lumen, and bubbles appeared in the beaker. In this case, the blocker cuff was inflated in 1-mL increments until air bubbles ceased to appear in the beaker, indicating bronchial seal, and the corresponding cuff volume was recorded.

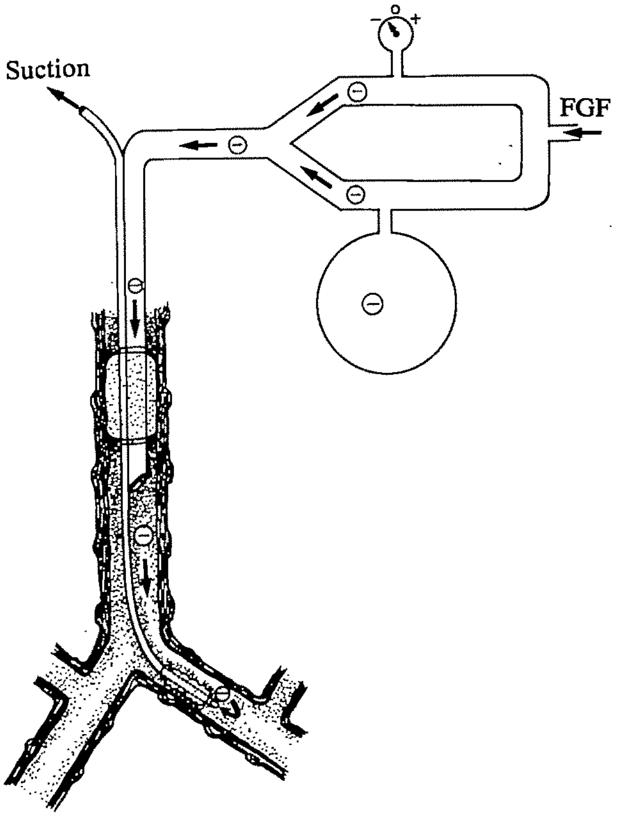

Figure 1. Negative pressure technique of bronchial cuff inflation. FGF, fresh gas flow. (Reproduced with permission from J. B. Lippincott Company; Hannallah M. The Univent® tube: bronchial cuff inflation. Anesthesiology 1991;75:165–6.)

Because the diameter of the blocker lumen is only 2 mm, spontaneous collapse of the blocked lung is very slow. To help lung collapse, suction through the blocker was maintained as long as the cuff was inflated regardless of whether the NPT or PPT was used.

Bronchial sealing volume as measured by NPT was used to inflate the blocker cuff, even if it was smaller than that measured by the PPT. After the chest was opened, the degree of collapse of the blocked lung was evaluated. If it was incomplete and the sealing volume as measured with the PPT was larger than that measured with the NPT, the cuff was inflated to the larger volume.

Fiberoptic confirmation of the position of the blocker was finally repeated to ensure that it remained completely within the bronchus after cuff

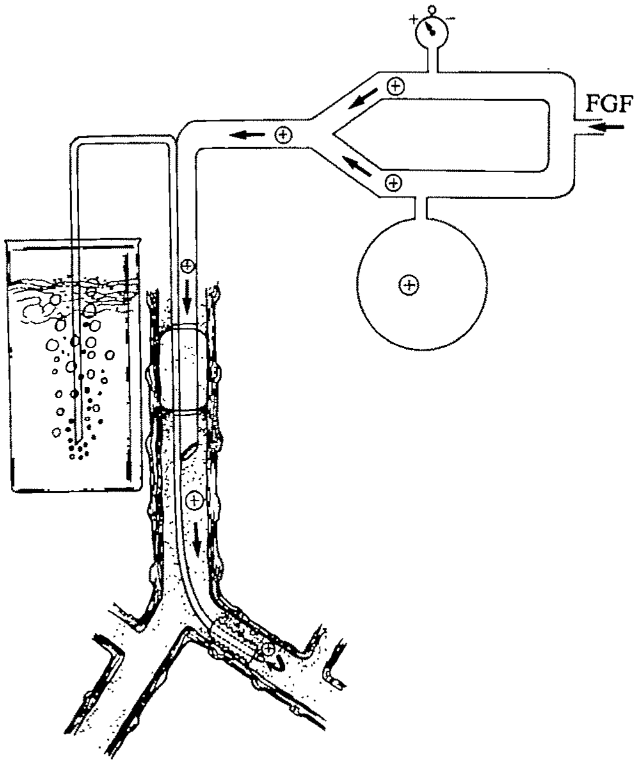

Figure 2. Positive pressure technique of bronchial cuff inflation. FGF, fresh gas flow.

inflation, because herniation of the cuff above the carina could compromise the seal and predispose to overinflation of the cuff.

Results

Figure 3 illustrates the relationship between cuff volume and mean cuff pressure in the four patients studied. The cuff was particularly noncompliant within the first 2 mL of inflation. At 2-mL volume, mean cuff pressure measured 178 mm Hg. For every 1-mL increase in cuff volume above 2 mL, mean cuff pressure increased by an average of 16 mm Hg.

Figure 4 illustrates the relationship between sealing volumes of the bronchial cuff as measured by both the NPT and PPT. The volume measured by the NPT ranged between 3 and 5 mL. When measured by the PPT, the volume range was 4–6 mL. The sealing volume measured by both techniques was equal in three patients. In the remaining five patients, the PPT failed to confirm bronchial seal when the cuff was inflated by the NPT. In these five patients, the cuff volume was increased by 1 mL before the PPT indicated bronchial seal.

In seven of the eight patients studied, complete collapse of the blocked lung was achieved when the bronchial cuff was inflated using the NPT. In the eighth patient, the sealing volume was 3 mL when measured by the NPT and 4 mL when measured by the PPT. The cuff was inflated to a volume of 3 mL initially. During thoracotomy, lung collapse was judged to be incomplete. When the cuff volume was increased to 4 mL, the lung became totally collapsed.

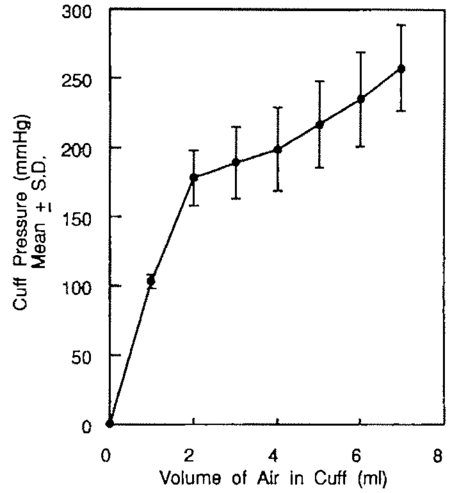

Figure 3. Compliance curve of the bronchial cuff of the Univent tube. Cuff pressure data are the mean ± SD in four patients.

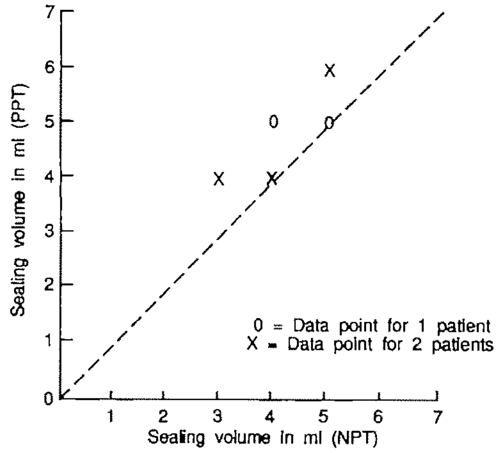

Figure 4. Relationship between sealing volumes of the bronchial cuff as measured by negative pressure technique (NPT) and positive pressure technique (PPT). *Dashed line* is line of identity.

Discussion

The high-pressure characteristics of the bronchial blocker cuff of the Univent tube was clearly demonstrated in this study. In a low-volume, high-pressure cuff, however, cuff pressure does not necessarily correlate to pressure exerted on the bronchial wall, because high pressure is needed to maintain cuff inflation itself (4,5). Nevertheless, intracuff pressure and pressure on the endobronchial wall can be expected to change in the same direction. In addition, more of the cuff pressure is likely to be transmitted to the endobronchial wall when contact between the two is complete, which takes place when a bronchial seal has been achieved. This emphasizes the importance of not inflating the cuff beyond its bronchial sealing volume.

Because no patient required a sealing volume of 7 mL, we tested the compliance curve of the blocker cuff in only four patients to avoid exposing more patients to unnecessarily higher cuff pressure than that which would produce bronchial seal.

Variable compliance at different cuff volumes could be explained by the fact that cuff pressure depends on the tension (T) in the cuff wall and on the cuff radius (R) at different cuff volumes, according to Laplace's law: $P = 2\,T/R$. The increase in cuff radius relative to the increase in wall tension must have been small at cuff volumes <2 mL, resulting in low compliance, and relatively larger at cuff volumes between 2 and 7 mL, resulting in better compliance. This is analogous to compliance and pressure changes of a reservoir bag in a breathing system that is progressively increasing in volume. The rate of rise in bag pressure decreases as its volume and diameter increase until the pressure inside the bag reaches a plateau of 40–50 cm H_2O as it continues to expand (6).

In this study, we sought to determine the optimal technique for inflating the cuff of the bronchial blocker of the Univent tube by comparing the two techniques that had been described for that purpose. We found that both techniques worked well and produced satisfactory lung collapse with the help of continuous suction through the blocker lumen. Complete collapse was well tolerated in the small group of patients studied. If hypoxemia results from the initiation of one-lung ventilation, suction can be discontinued, and constant positive airway pressure can be applied to the operative lung through the blocker lumen to correct it (7).

The NPT could achieve lung collapse with cuff volume that was sometimes 1 mL smaller than that measured by the PPT. That could possibly be explained by the fact that the endpoint for the PPT is more sensitive than that for the NPT. It is easier to see a few small bubbles under water than to detect a minor change in the volume of a 3-L reservoir bag. The difference in bronchial sealing volumes between the two techniques may also be due to a difference in lung volume and airway caliber at the time of bronchial cuff inflation. At that time, the lungs and airways are maximally expanded when the PPT is used and are in a neutral or partially collapsed position when the NPT is used. Reducing cuff volume by 1 mL reduces cuff pressure by 16 mm Hg on average. The value of this magnitude of pressure reduction when cuff pressure is already in the 200–250 mm Hg range is probably not significant.

The 1-mL incremental change in cuff volume was chosen in this study because it was considered a small but still clinically significant change. If cuff volume were increased in <1-mL increments, the differences between bronchial sealing volumes of the cuff as measured by the two techniques would probably be <1 mL.

In conclusion, the Univent tube bronchial blocker cuff is a high-pressure cuff that should be inflated carefully to the smallest bronchial sealing volume. Both the PPT and the NPT can be used satisfactorily for that purpose. The NPT is easier to perform, requires fewer tools, and usually uses a slightly smaller volume of air in the cuff. Gas-tight bronchial seal against known airway pressure is more reliably produced with the PPT, which may therefore provide better lung protection in the presence of bleeding or infection.

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Tracheal Intubation Without the Use of Muscle Relaxants: A Technique Using Propofol and Varying Doses of Alfentanil

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We have noted that tracheal intubation can be accomplished in many patients after induction of anesthesia with propofol and alfentanil without the simultaneous use of muscle relaxants. This study was designed to evaluate airway and intubating conditions after administration of propofol and alfentanil in 75 ASA physical status I or II outpatients with Mallampati class I airways undergoing various surgical procedures. The patients were randomly assigned to one of five groups for induction of anesthesia. All patients received midazolam 1 mg IV before induction of anesthesia. Group I patients (n = 15) received d-tubocurarine 3 mg, thiamylal 4 mg/kg, and succinylcholine 1 mg/kg IV. Groups II–V patients (n = 15 each) received alfentanil 30, 40, 50, or 60 μg/kg followed by propofol 2 mg/kg IV. No muscle relaxants were given to patients in groups II–V. Airway management was performed by one of the authors who was blinded as to the dose of alfentanil administered. After loss of consciousness, patients' lungs were ventilated via face mask, and the ease of ventilation was recorded. Jaw mobility was also assessed. Ninety seconds after administration of the propofol or thiamylal, laryngoscopy was performed and exposure of the glottis and position of the vocal cords were noted. Intubation of the trachea was performed and patient response was noted. Heart rate and arterial blood pressure were also recorded before induction of anesthesia, after induction, and then again after intubation of the trachea. The lungs of all patients were easily ventilated via mask, and the jaw was judged to be relaxed in all patients. In group II (30 μg/kg alfentanil), 5 of 15 patients' tracheas could not be intubated because of poor exposure of the cords or the presence of closed vocal cords. In all other groups, vocal cord position was significantly more often favorable for tracheal intubation compared with the 30 μg/kg alfentanil group. In patients given alfentanil, the incidence of persistent coughing or movement after intubation of the trachea was most frequent with the 30-μg/kg dose of alfentanil. All patients receiving alfentanil had significant decreases in heart rate and arterial blood pressure after induction of anesthesia compared with preinduction values. However, there were no differences between the alfentanil groups. Patients who received thiamylal and succinylcholine had significant increases in heart rate after induction of anesthesia compared with preinduction values. Mean arterial pressure increased significantly after laryngoscopy and intubation of the trachea compared with postinduction values in patients receiving thiamylal and succinylcholine. We conclude that in premedicated outpatients with favorable airway anatomy receiving alfentanil (>30 μg/kg) and propofol for induction, ventilation via mask, jaw mobility, exposure of the vocal cords, position of the cords during laryngoscopy, and patient response to intubation of the trachea differs little from that achieved with thiamylal and succinylcholine.

(Anesth Analg 1992;75:788–93)

Induction of anesthesia using short-acting hypnotic drugs is frequently facilitated by the simultaneous administration of a depolarizing muscle relaxant such as succinylcholine. However, succinylcholine administration may be associated with side effects such as prolonged paralysis, postoperative myalgias, malignant hyperthermia, hyperkalemia, or increases in intracranial or intraocular pressure (1). These side effects have spurred research into the development of a nondepolarizing drug with a short onset of action. One of these, mivacurium, has recently been approved by the Food and Drug Administration and is now available for clinical use. However, even the use of nondepolarizing relaxants may be associated with undesirable effects, such as prolonged neuromuscular blockade, the need to reverse neuromuscular blockade, or the inability to reverse the paralysis quickly if airway management via mask or tracheal intubation is not possible. For these reasons, a method of providing good intubating conditions rapidly without using muscle relaxants has been sought by a number of investigators. Thiopental

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alone in the dose of 4 mg/kg has been summarily judged to provide poor intubating conditions (2). Propofol, on the other hand, has been reported to depress pharyngeal and laryngeal reactivity to a greater extent than equipotent doses of thiopental (3). When either propofol or thiopental were combined with alfentanil (30 μg/kg) and lidocaine 1.5 mg/kg, jaw relaxation, visualization of the larynx, position of the vocal cords, ease of tracheal intubation, and tolerance of the endotracheal tube were observed to be favorable in the majority of patients (4). Nonetheless, the authors of this study recommended against routine use of this technique, because they believed it could not guarantee the excellent intubating conditions generally associated with the use of succinylcholine and thiopentone.

We too have noted that in outpatients given propofol and alfentanil for anesthetic induction, the lungs are easily ventilated via face mask, and laryngoscopy and tracheal intubation are easily performed without the need for concomitant neuromuscular blockade. The purpose of the present study was to characterize airway management, tracheal intubation, and hemodynamic responses in patients with favorable airway anatomy given varying doses of alfentanil in the presence of a fixed dose of propofol and to compare the results with those obtained with a standard thiamylal/succinylcholine induction sequence.

Methods

We studied 75 surgical patients undergoing same-day surgery for a variety of surgical procedures for which endotracheal anesthesia was planned. The study was approved by the institutional human studies review board. Patients were ASA physical status I or II, and all had Mallampati class I airway anatomy (5). Patients were excluded if they had a history of intravenous drug use, alcohol addiction, full stomach, coronary artery disease, or reactive airway disease.

Once in the operating room, intravenous access was established and all patients received 1 mg of midazolam intravenously. After midazolam administration, patients were asked to breathe oxygen via face mask while baseline vital signs (preinduction) were measured. Monitors included an automated blood pressure cuff, electrocardiogram, transcutaneous pulse oximeter, temperature, and end-tidal carbon dioxide. Patients were randomized to one of five groups by having an assistant pick one of five cards describing the induction sequence. Group I patients (n = 15) received *d*-tubocurarine 3 mg, thiamylal 4 mg/kg, and succinylcholine 1 mg/kg. Group II patients (n = 15) received alfentanil 30 μg/kg and propofol 2 mg/kg. Group III patients (n = 15) received alfentanil 40 μg/kg and propofol 2 mg/kg. Group IV patients (n = 15) received alfentanil 50 μg/kg and propofol 2 mg/kg. Group V patients (n = 15) received alfentanil 60 μg/kg and propofol 2 mg/kg. No muscle relaxants were given to patients in groups II–V. Ventilation via mask, laryngoscopy, and tracheal intubation were performed by an experienced anesthesiologist (one of the authors) who was unaware as to the dose of alfentanil the patient would be given. (Note that we were not able to be completely blinded as to group because we could generally distinguish the thiamylal/succinylcholine group from the others.) Alfentanil was delivered as a bolus infusion by a battery-powered pump (model AS20GH-2; Baxter Health Care Corporation, Hooksett, N.H.) which was programmed with the patient's weight and the dose of alfentanil. Methylene blue (0.1 mL) was added to the alfentanil as a marker to ensure the accurate delivery of alfentanil in all cases. The pump required approximately 80 s to deliver a 40-μg/kg bolus to a 60-kg patient. When the alfentanil bolus was finished, propofol (2 mg/kg) was given as a rapid intravenous bolus by hand-held syringe. Once the patient lost consciousness, ventilation via mask was attempted and the ease of ventilation was recorded as easy, difficult, or impossible. Vital signs were measured 45 s after the bolus dose of propofol was given (postinduction). Oral or nasal airways were inserted at the discretion of the anesthesiologist. Ninety seconds after the propofol was administered, laryngoscopy was attempted by one of three experienced anesthesiologists who was unaware of the dose of alfentanil given. During laryngoscopy and attempted intubation of the trachea, the intubating anesthesiologist assessed each patient for four variables: jaw relaxation, exposure of the vocal cords, position of the vocal cords, and patient movement during and within 1 min of attempted intubation of the trachea. The criteria used for ranking these variables are listed in Table 1. Patients whose tracheas could not be intubated after receiving the assigned induction drugs were so noted and succinylcholine (1 mg/kg IV) was administered. Tracheal intubation was then reattempted and exposure of the larynx and outcome of the intubation attempt were recorded. Once the trachea was intubated, the tracheal cuff was gently inflated. Vital signs were obtained immediately (postintubation) and recorded. Anesthesia was maintained at the discretion of the anesthesia care provider.

Mean arterial pressure and heart rate data were analyzed by one-way analysis of variance with post hoc paired *t*-testing where appropriate, comparing changes from preinduction values to postdrug and posttracheal intubation values within groups. Two-way analysis (group vs time) of variance was used to

Table 1. Scoring Criteria for Various Airway Conditions and Responses

Score	Criteria
Jaw Mobility	
1	Jaw mobile
2	Jaw partly mobile
3	Jaw immobile
Mask Ventilation	
1	Mask ventilation easy
2	Mask ventilation difficult
3	Mask ventilation impossible
Exposure	
1	Vocal cords and arytenoids completely visible
2	Vocal cords or arytenoids partly visible
3	Vocal cords or arytenoids not seen
Cord Position	
1	Vocal cords open
2	Vocal cords midposition
3	Vocal cords closed
Movement	
1	No movement
2	One or two coughs
3	Persistent coughing
4	Purposeful movement
Trachea Intubatable Without Additional Drugs Given?	
1	Yes
2	No

test for differences in heart rate and mean arterial pressure between groups. Kruskal-Wallis and χ^2 analyses were used to determine differences between groups for nonparametric data.

Results

There were no significant differences between groups in terms of gender distribution, mean patient weight, mean patient age, or the percentage of smokers (Table 2). There were no significant preinduction differences between groups in heart rate or mean arterial blood pressure (Table 3). Mean arterial pressure and heart rate decreased significantly after induction compared with preinduction values in patients who received alfentanil (groups II–V) (Table 3). However, the magnitude of the postinduction decreases in heart rate and mean arterial blood pressure were not different between the various groups of patients who received alfentanil. Postintubation mean arterial pressure increased significantly compared with postinduction values in all of the groups receiving alfentanil. Group I patients (thiamylal/succinylcholine) had significant increases in heart rate after induction compared with preinduction values. Mean arterial pressure also increased significantly after intubation compared with postinduction values in group I patients (Table 3).

The ease with which ventilation via mask could be performed was not different between groups. In no patient was ventilation via mask judged to be impossible. In one patient in the 30-μg/kg group and in two patients in the 40-μg/kg group, the lungs were thought to be difficult to ventilate via mask. Jaw relaxation was thought to be good in all patients. No patient appeared to manifest signs of opioid-induced rigidity at any time. Exposure of the glottis was more often judged to be complete in groups I, III, IV, and V compared with group II (30 μg/kg alfentanil). However, these differences were not statistically significant. Exposure of the vocal cords was either complete (12/15) or partial (3/15) in all patients receiving thiamylal/succinylcholine. Complete or partial vocal cord exposure was judged to be absent in one patient in each of the alfentanil groups. However, the one patient receiving 60 μg/kg in whom the vocal cords could not be even partially visualized and in whom the initial attempt at tracheal intubation was unsuccessful then received succinylcholine 1 mg/kg. Repeat laryngoscopy was also not successful at exposing any part of the vocal cords, although the trachea was intubated by passing the tube blindly posterior to the epiglottis. In one patient receiving 50 μg/kg in whom the vocal cords could not be even partially visualized, the trachea was successfully intubated on the first attempt. No coughing or movement was observed in that patient after tracheal intubation and inflation of the endotracheal cuff.

The position of the vocal cords during laryngoscopy was significantly more often judged to be open or midposition in patients receiving 40, 50, or 60 μg/kg of alfentanil or thiamylal/succinylcholine compared with patients receiving 30 μg/kg (P = 0.023, 0.016, 0.029, and 0.018, respectively). In groups III, IV, and V (40–60 μg/kg alfentanil), there were no significant differences between groups with respect to vocal cord position (Table 4). One patient exhibited purposeful movement after intubation of the trachea. That patient received 40 μg/kg of alfentanil. The patient moved her hand but did not cough or otherwise object to the presence of the endotracheal tube in her trachea and had no recall of the event when questioned later. No patient in the 50- or 60-μg/kg alfentanil group or the thiamylal/succinylcholine group moved purposefully in the periinduction period. After intubation of the trachea and inflation of the tracheal cuff, a small number of patients in every group coughed persistently. Three patients in the 30-μg/kg alfentanil group, three in the

Table 2. Patient Characteristics

	Dose of alfentanil				
	30 μg/kg	40 μg/kg	50 μg/kg	60 μg/kg	Sux/Thiam
Male/female	5/10	4/11	2/13	5/10	7/8
Age (yr)	33 ± 9	30 ± 10	35 ± 11	36 ± 16	37 ± 10
Weight (kg)	65 ± 11	66 ± 15	66 ± 12	68 ± 16	77 ± 20
Smoker/non	4/11	4/11	1/14	2/13	4/11

Sux/Thiam, succinylcholine/thiamylal.
Age and weight expressed as mean ± SD.
There were no differences between groups.

Table 3. Mean Arterial Pressure and Heart Rate Responses to Drug Administration and Tracheal Intubation

	Preinduction		Postinduction		Postintubation	
Groups	MAP	HR	MAP	HR	MAP	HR
ALF 30 μg/kg (n = 15)	91 ± 8	72 ± 12	67 ± 10[a]	63 ± 9[a]	81 ± 17[b]	68 ± 14
ALF 40 μg/kg (n = 15)	86 ± 12	73 ± 14	64 ± 10[a]	63 ± 9[a]	75 ± 15[b]	67 ± 13
ALF 50 μg/kg (n = 15)	94 ± 11	72 ± 13	64 ± 10[a]	64 ± 10[a]	77 ± 8[b]	65 ± 11
ALF 60 μg/kg (n = 15)	95 ± 13	73 ± 11	64 ± 10[a]	66 ± 11[a]	72 ± 10[b]	67 ± 13
Sux/Thiam (n = 15)	98 ± 13	81 ± 15	105 ± 18	96 ± 16[c]	132 ± 16[b]	104 ± 14

ALF, alfentanil; Sux/Thiam, succinylcholine/thiamylal; MAP, mean arterial blood pressure; HR, heart rate.
All data are mean ± SD.
[a] Denotes significant decrease from preinduction value.
[b] Denotes significant increase from postinduction value.
[c] Denotes significant increase from preinduction value.
$P < 0.05$ considered significant in all cases.

40-μg/kg alfentanil group, and one in the thiamylal/succinylcholine group had persistent coughing after tracheal intubation and inflation of the cuff. No patient in the 50-μg/kg alfentanil group or the 60-μg/kg alfentanil group had persistent coughing (Figure 1). A number of patients coughed once or twice after inflation of the tracheal cuff, but this was not drug or dose related. Of the 15 patients receiving thiamylal/succinylcholine for induction, four patients coughed once or twice after tracheal intubation and cuff inflation. The numbers of patients in groups II–V who coughed once or twice were 2, 4, 7, and 3, respectively (Figure 1). Significantly more patients (5 of 15) in group II (30 μg/kg) required succinylcholine for eventual tracheal intubation compared with all of the other alfentanil groups in which only 1 patient (60 μg/kg) required succinylcholine for tracheal intubation.

One patient who received thiamylal/succinylcholine had prolonged neuromuscular blockade lasting approximately 2.5 h after a 20-min laparoscopy. However, plasma cholinesterase levels and dibucaine number were in the normal range in this patient, leading us to suspect that this patient has a rare form of atypical acetylcholinesterase.

Discussion

These data demonstrate that tracheal intubation may be accomplished reliably in premedicated outpatients with favorable airway anatomy after intravenous induction without the simultaneous administration of muscle relaxants. Others have also reached similar, but not identical conclusions. For example, Kallar (3) was able to intubate the tracheas of 28 of 30 patients who were given 4 μg/kg of fentanyl, 1 mg/kg of lidocaine, and 2.5 mg/kg of propofol. This compared with 1 of 30 patients given fentanyl, lidocaine, and 4 mg/kg of thiopental and 0 of 30 patients given fentanyl, lidocaine, and 2 mg/kg of methohexital. Havorka et al. (4) studied 106 patients given 1.5 mg/kg of lidocaine and 30 μg/kg of alfentanil who

Table 4. Position of the Vocal Cords During Laryngoscopy

	Vocal cord position			
	Closed	Midposition	Open	Not determined[b]
ALF 30 µg/kg (n = 15)[a]	6	3	6	0
ALF 40 µg/kg (n = 15)	0	5	10	0
ALF 50 µg/kg (n = 15)	0	2	12	1
ALF 60 µg/kg (n = 15)	0	5	9	1
Sux/Surital (n = 15)	0	3	12	0

ALF, alfentanil; Sux, succinylcholine.
[a] Denotes 30-µg/kg group different from all others by χ^2 analysis.
[b] Number of patients in whom vocal cord position could not be determined.

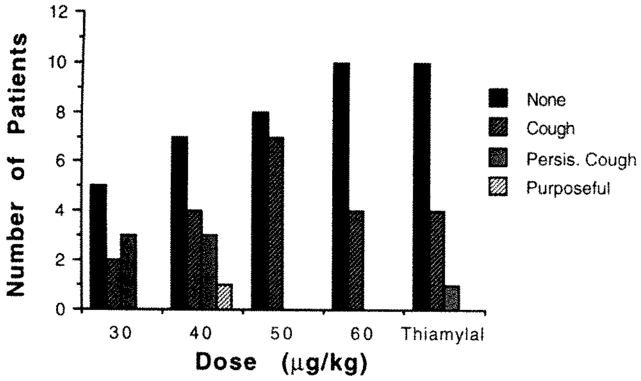

Figure 1. Response to tracheal intubation. *None* denotes no coughing or movement. *Cough* denotes one or two coughs after insertion of tracheal tube. *Persis. Cough* denotes three or more coughs. *Purposeful* denotes purposeful movement during or after tracheal intubation.

were then assigned to receive either propofol 2.5 mg/kg or thiopental 5 mg/kg for induction. They noted that tracheal intubation was more easily accomplished with thiopental than with propofol. Although Havorka et al. did not study a group of patients receiving succinylcholine, they concluded that intubating conditions were not reliably acceptable with either propofol or thiopental, and that succinylcholine or other muscle relaxants should be used routinely to ensure optimal intubating conditions. It should be pointed out, however, that Havorka et al. found that tracheal intubation was difficult in only 1 patient in 50 who received thiopental and 5 of 50 who received propofol.

Our study differed from that of Havorka et al. in that we included control groups of patients who received more than 30 µg/kg of alfentanil. Our results agree with those of Havorka et al. in that administration of thiamylal/succinylcholine was associated with better exposure of the vocal cords and a significantly reduced incidence of closed or midposition vocal cords compared with 30 µg/kg of alfentanil. In fact, we had a substantially higher percentage of patients (5 of 15) in the 30-µg/kg group who eventually required succinylcholine for tracheal intubation than Havorka et al. This may be attributable to methodologic differences in the two studies, as we did not include lidocaine in our premedication and our induction dose of propofol was 25% less. However, the results we obtained with higher doses of alfentanil were not objectively or subjectively different from those obtained using thiamylal/succinylcholine. Specifically, exposure of the vocal cords, position of the vocal cords during laryngoscopy, and patient movement during or after tracheal intubation were not different between the groups of patients receiving 40, 50, or 60 µg/kg of alfentanil and the group receiving thiamylal/succinylcholine. Similarly, in terms of intubation parameters, there were no differences between the 40-, 50-, and 60-µg/kg alfentanil groups, suggesting that doses of alfentanil above 40 µg/kg will not be associated with better intubating conditions.

No patient receiving alfentanil was thought to exhibit signs of opioid-induced muscular rigidity. The jaw was judged to be relaxed in all patients and the lungs of all but two patients could be easily ventilated via mask. In no patient was ventilation via mask deemed impossible. The ED_{50} for induction with alfentanil is approximately 110 µg/kg in healthy patients (6). That is, approximately 50% of patients will lose consciousness with that dose of alfentanil. In that study, chest wall rigidity was observed in 4 of 7 patients given 100 µg/kg of alfentanil, although no patient recalled any difficulty breathing. Because our dose range, 30–60 µg/kg, was well below the ED_{50} for induction for alfentanil, we did not expect rigidity to be a clinical problem. We also administered midazolam and propofol in combination with the alfentanil. There is evidence in animals and humans that benzodiazepines and barbiturates do prevent or attenuate alfentanil-induced muscular rigidity (7–9). Propofol may have similar properties, but this has not been studied as of yet. The slow rate of infusion of the alfentanil bolus dose may also have made opioid-induced rigidity less likely.

Arterial blood pressure and heart rate decreased significantly in patients given alfentanil (regardless of dose), whereas arterial blood pressure and heart rate increased in patients given thiamylal/succinylcholine. The administration of opioids was expected to be associated with lower arterial blood pressure and heart rate compared with thiamylal and succinylcholine. This has been observed by other investigators using a variety of induction techniques (10). Despite mean arterial pressures in the 50–60 mm Hg range in some patients after a propofol/alfentanil induction sequence, we did not administer ephedrine to any patient. Our experience has been that this relative hypotension is always associated with good peripheral perfusion, as evidenced by continuing digital pulse oximetry readings, and is short lived. Intubation of the trachea is almost always followed by an increase in arterial blood pressure (Table 3). However, our patient population was relatively young and healthy, and this technique may not be appropriate for some elderly or hypovolemic patients or for patients with some forms of cardiovascular or cerebrovascular disease.

Of concern to many anesthetists is the state of the patient immediately after the trachea has been intubated. Our observation period after intubation was only 1 min long, and in that period of time we noted very few patients moving purposefully or coughing persistently. It must be pointed out, though, that unless supplemental anesthesia is quickly administered, some patients will begin to cough or move within a few minutes, particularly in response to surgical positioning or preparation. Thus, when using this technique for tracheal intubation, additional anesthetic drugs such as nitrous oxide, isoflurane, propofol, or thiopental should be administered soon after induction to reliably prevent coughing or movement.

Along these lines, it must be pointed out that we waited 90 s after administering alfentanil before attempting laryngoscopy. We chose this period of time because of electrophysiologic data suggesting that the peak effect of alfentanil occurred at approximately 90 s after a bolus dose (11,12). Using a different waiting period might produce results different from those we observed.

We conclude that in premedicated healthy outpatients with favorable airway anatomy, tracheal intubation may be accomplished using a combination of 40 μg/kg of alfentanil and 2 mg/kg of propofol. The simultaneous administration of muscle relaxants may not be necessary to ensure acceptable jaw mobility, mask ventilation, vocal cord exposure, vocal cord position, or movement in response to tracheal intubation in this patient population. Because muscle relaxant administration may be associated with undesirable side effects, this technique may be of value in some patients.

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Comparison of the Anesthetic Requirement for Tolerance of Laryngeal Mask Airway and Endotracheal Tube

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We tested the hypothesis that the laryngeal mask airway (LMA) is tolerated at lighter levels of anesthesia than an endotracheal tube (ET). We studied 20 unpremedicated, nonsmoking ASA physical status I or II patients aged 18–40 yr whose surgery lasted >1 h. Subjects were randomly assigned to receive either an ET or LMA. Anesthesia was induced with intravenous propofol and the LMA or ET was inserted. The ET-group patients received 1.5 mg/kg of succinylcholine, preceded by vecuronium (0.015 mg/kg IV). Maintenance of anesthesia was with only isoflurane and approximately 66% N_2O in O_2 by spontaneous ventilation. All gas concentrations were measured by a Raman spectrometer sampling from the breathing circuit end of the LMA or ET. Toward the end of the procedure, the end-tidal N_2O and isoflurane concentrations were allowed to decrease to <3 vol% and 0.8 ± 0.05 vol%, respectively. The end-tidal isoflurane concentration was then decreased in 0.1% ± 0.05% decrements, each stable value being held for 5 min. The patient was observed for signs of reaction to the presence of the LMA or ET. The mean (range) end-tidal isoflurane concentrations for reaction to ET and LMA were 0.55% (0.4–0.7) and 0.35% (0.2–0.51), respectively ($P < 0.001$). These data confirm the original hypothesis of the study.

(Anesth Analg 1992;75:794–7)

A major responsibility of the anesthesiologist in caring for the anesthetized patient is ensuring patency of the airway and adequacy of ventilation. Problems may occur during light anesthesia (coughing, breath holding, and airway obstruction from soft tissues, laryngeal spasm, and bronchospasm); during deep anesthesia (hypercarbia and hypoxia from respiratory depression); or at any level of anesthesia (all of the above plus inability to intubate the trachea and the presence of foreign material in the respiratory tract).

These problems may be overcome in a number of different ways. A novel approach to avoid, or better manage, some of them is the use of the laryngeal mask airway (LMA) developed by Brain (1,2). The LMA (Intavent International, The Netherlands) is inserted blindly through the mouth and forms an airtight seal against the perimeter of the larynx after inflation of the elliptical cuff within the hypopharynx (1,2). One of its specific advantages is its capacity to provide a clear airway in patients in whom conventional mask anesthesia is difficult or impossible and in whom tracheal intubation is either difficult or undesirable. Controlled ventilation through the LMA is usually successful (3), but the device does not protect the airway from aspiration of gastric contents.

Clinical experience suggests that the LMA is tolerated at much lighter levels of anesthesia than are required for the presence of an endotracheal tube (ET). This could be of twofold advantage: first, it might allow lighter levels of anesthesia to be used in some circumstances; second, it would circumvent the repetitive breath holding and coughing that sometimes occur when patients awaken with an ET in place. It is this putative advantage that we tested in this study.

Methods

Approval of the Oregon Health Sciences University Committee on Human Research was obtained, and all subjects gave written, informed consent before their inclusion in the study. Twenty (11 male, 9 female) ASA physical status I or II patients aged 18–40 yr were selected. All were of normal body weight and airway examination and were free from factors predisposing them to inhalation of gastric contents. Patients were nonsmokers, free from sub-

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stance abuse, and were not on incidental drug therapy. The following criteria were also met:

1. An operation requiring the supine position
2. An operation allowing unrestricted access to the patient's head and neck throughout anesthesia
3. An operation not involving penetration of a serous cavity or the use of neuromuscular blocking drugs
4. An operation that could be performed with equal safety using inhaled anesthesia administered through either an LMA or ET
5. A procedure expected to last 1–2 h.

Such procedures included a variety of gynecologic, orthopedic, plastic, and general surgical procedures.

Patients were unpremedicated. Each was randomly assigned (on the basis of the last digit of the hospital registration number) to receive either an LMA (n = 10) or ET (n = 10). After institution of appropriate monitoring and breathing oxygen, anesthesia was induced with propofol (2.0–2.5 mg/kg IV) over approximately 30 s until the eyelash reflex was lost. Patients allocated to the ET group also received succinylcholine (1.5 mg/kg IV), preceded by vecuronium (0.015 mg/kg IV) to reduce muscle fasciculations. Patients in the LMA group did not receive any neuromuscular blocking drugs. The LMA or ET was then inserted in the usual way. Ventilation was assisted until the return of adequate spontaneous respiration. Anesthesia was maintained with isoflurane in approximately 66% N_2O in O_2 administered through a circle CO_2 absorption system at a total fresh gas inflow of 6 L/min, and the concentration of isoflurane was adjusted in response to clinical signs. No other drugs were administered.

At the end of the surgical procedure, the N_2O flow was discontinued, and anesthesia was maintained with isoflurane in O_2. The end-tidal N_2O concentration was allowed to decrease <3% for 5 min. The patient was left completely undisturbed during the following sequence.

The end-tidal isoflurane concentration was reduced in decrements by manipulation of the vaporizer setting. The initial value was 0.8% ± 0.05%, and each decrement was 0.1% ± 0.05%. Each concentration was maintained for 5 min after both (a) the end-tidal value had been reached, and (b) the difference between the inspired and end-tidal concentrations was <25% of the end-tidal concentration.

The patient was continuously observed for signs of reaction to the presence of the LMA or ET. Such signs were swallowing, coughing, gagging, sudden changes in the depth or regularity of respiration, movement of the head, or gross purposeful movement to remove the device. Shivering or extensor posturing were regarded as ambiguous signs, and the patient exhibiting these was excluded from analysis.

The occurrence of one or more of these signs was taken as the endpoint of the study, and the end-tidal isoflurane concentration at which it occurred was taken to be the value for intolerance of the airway device. The LMA or ET was then removed according to clinical judgment.

Monitoring of respired gas concentrations was with Raman gas analysis (Rascal, Albion Instruments, Salt Lake City, Utah), sampling continuously from the junction of the breathing attachment and the LMA or ET. This instrument provides values of inspired and expired concentrations of O_2, CO_2, N_2, N_2O, and volatile anesthetics. Values for volatile anesthetics are given to two decimal places. The calibration was checked, after the machine had been running for at least 1 h, against three reference standards (0.31% isoflurane in O_2; 2% isoflurane in 40% N_2O/balance O_2; and pure argon) before each procedure. A full calibration was performed if the error for isoflurane concentration was greater than ±0.01% against the 0.31% reference or >0.1% against the 2% reference value. During the emergence sequence, inspired and expired N_2 concentrations were recorded as a means of detecting atmospheric contamination (leak).

Statistical analysis was by Fisher's exact test, to test for bias in the distribution of ET and LMA between genders and to confirm randomization, and by Student's t-test for other data. The level of significance was taken at $P < 0.05$.

Results

Twenty patients participated in the study (11 male, 9 female). Ten received an LMA and 10 an ET. Two patients in the ET group were eliminated from the study, one because of shivering movements at the end of the procedure and one who received opiate analgesia during surgery. There were no significant differences between the groups for age, gender distribution, duration of N_2O exposure, propofol dosage, and time between attainment of the final end-tidal isoflurane concentration and the time of rejection of the LMA or ET (Table 1). There were no differences between the groups for end-tidal CO_2 values at both the beginning and end of the measurement period (Table 1). No bias in distribution of LMA or ET by hospital number was detected.

In all cases, the goal of obtaining the difference between the inspired and end-tidal isoflurane concentrations at <25% of the end-tidal value was bettered, the maximal deviation being 10% during the stepwise reduction of isoflurane concentration and 25% for the final values at the point of airway rejection. In all cases, this point was reached before the full 5-min stabilization period had been achieved.

Table 1. Clinical Characteristics of the 18 Study Patients

	LMA group	ET group
Age (yr)	30.8 (9.6)	26.1 (8.1)
Gender (M/F)	7/3	4/4
Propofol (mg/kg)	3.1 (1.4)	3.5 (0.88)
N_2O exposure (min)	84.7 (22.4)	99.7 (28.0)
Time at final isoflurane conc. (s)[a]	184 (47.1)	167 (36.7)
$P_{\mathrm{ET}}\mathrm{CO}_2$ (mm Hg)		
Start	45.4 (11.2)	43.7 (11.9)
End	40.8 (6.2)	41.4 (5.7)

LMA, laryngeal mask airway; ET, endotracheal tube; conc., concentration; $P_{\mathrm{ET}}\mathrm{CO}_2$, end-tidal CO_2.

Values are mean (SD); gender distribution by absolute numbers.

[a] Before rejection of the LMA or ET.

Table 2. Inspired and End-Tidal Concentrations of Isoflurane at the Time of Reaction to the LMA or ET

	LMA group	ET group
End-tidal conc. (%)	0.35 (0.11)	0.55 (0.09)[a]
Inspired conc. (%)	0.31 (0.12)	0.56 (0.07)[a]

LMA, laryngeal mask airway; ET, endotracheal tube; conc., concentration.

Values are mean (SD).

[a] ET > LMA ($P < 0.001$).

The signs indicating rejection of the airway device were always swallowing, coughing, or biting, sometimes accompanied by movements of the head rather than changes in the depth or regularity of respiration. Data for isoflurane concentrations were found to be normally distributed and are shown in Table 2.

Discussion

The LMA was introduced into clinical practice by Brain (1,2). Its use is well documented in the anesthetic literature (1–5). One of its claimed advantages is that its presence causes very little stimulation and that it is tolerated at light levels of anesthesia (LMA User's Manual, Intavent International). In contrast, the presence of an ET may necessitate a deeper level of anesthesia, which may cause hypoventilation in patients breathing spontaneously. This may alter the choice of anesthetic technique in favor of controlled ventilation in tracheally intubated patients. It is also likely that an airway device that is tolerated at light levels of anesthesia would provoke fewer episodes of coughing, breath holding, and bronchospasm during emergence than one requiring deeper levels of anesthesia. The use of lighter levels of anesthesia may also result in less cardiovascular depression and shorter recovery times.

All observations were made by a single observer who was aware of the nature of the airway device used. This is unlikely to cause bias, because the clinical signs used (coughing, biting, swallowing) were distinct and easy to observe.

The randomization was by last digit of hospital number. This method was used for simplicity but may have been a source of unrecognized bias. However, analysis of the distribution has not shown any such problem (Fisher's exact test).

The end-tidal isoflurane concentration was allowed to decrease in steps of 0.1%, and the point at which reaction to the presence of the airway device occurred was taken as the endpoint of the study. Each concentration was held constant for 5 min after the difference between the inspired and end-tidal concentrations was <25% of the end-tidal value. This favors equilibration of end-tidal, alveolar, and arterial concentrations and results in an error of <5% in the alveolar concentration as an estimate of the arterial value (6). Although each concentration was maintained for 5 min, it was clearly not possible to control the point of airway rejection, and therefore the time at the final concentration also could not be controlled. The "true" end-tidal concentration at which the patient would have reacted to the presence of the airway device is thus underestimated. Furthermore, because the equilibration time was only 5 min, the alveolar partial pressure of isoflurane as an estimate of brain tension will also be an underestimate (7). The 5-min period was chosen as a compromise between absolute accuracy and an unacceptable prolongation of the patient's anesthetic. The gas analyzer sampled from the junction of the breathing attachment and the LMA or ET. It is therefore possible that the samples were not truly end-tidal. For all these reasons, it was not considered meaningful to calculate MAC values for rejection of the airway devices. Nevertheless, the validity of the observed difference between the groups should not be affected by these factors.

Because the LMA may not form a gas-tight seal with the airway, it is possible that leakage of gas could have occurred. Contamination with air during inspiration would result in a lower concentration of isoflurane being delivered to the alveoli than the measured inspired value. We measured N_2 concentrations in the expired gas, and none was detected in any patient. A leak during inspiration is therefore unlikely.

Leakage during expiration, particularly if it occurred at the end of expiration, would produce a falsely low measured value, because anesthetic would be lost before it could be measured. Grouped data for inspired and end-tidal isoflurane concentrations are shown in Table 2. Inspired and end-tidal values are similar within the groups, and for the LMA group, the end-tidal concentration is greater than the inspired concentration. This suggests that significant leakage did not occur. This is further supported by the CO_2 concentrations, which were not significantly different between the groups (Table 1).

Propofol was chosen over thiopental as the drug used to induce anesthesia for two reasons. First, clinical experience suggests that passage of the LMA is smoother when propofol is used. Second, its shorter elimination half-life should make it less likely to affect anesthetic requirements during the measurement period >1 h after administration; however, this effect cannot be excluded.

The total propofol dosage was more than expected. This may reflect the fact that the patients were unpremedicated, and several appeared overtly anxious. Four patients in each group required supplemental propofol to prevent movement immediately after induction. Propofol dosage was not different between the groups.

N_2O was used during surgery but discontinued before the start of the observation sequence. Washout of N_2O from the brain is rapid (half-time 1.6 min) and will lag behind both the blood and alveolar compartments. To be certain that any residual anesthetic effect of N_2 had been minimized, the alveolar (end-tidal) concentration was allowed to decrease to <3% for 5 min.

Bench testing of the model of the type of Raman scattering detector that we used has shown the instrument to be capable of accuracy in measurement of volatile anesthetic concentrations of ±0.03% (8). An evaluation in the clinical setting has shown it to be as accurate in measuring volatile anesthetic concentrations as a dedicated mass spectrometer (9). The manufacturer quotes an accuracy for clinical use of only ±0.3% for volatile anesthetics. This is to allow for variation between instruments and drift from calibration that is only performed monthly, as well as for using the instrument before full warm-up. We used a single instrument for all cases and verified the accuracy of the instrument before each use after allowing a period for full warm-up. We accepted an accuracy of ±0.01% at 0.31% isoflurane and 0.1% at 2% isoflurane. Thus, although absolute accuracy of the concentrations cannot be guaranteed, the observed difference between the groups remains valid.

We conclude that the LMA is tolerated at lower concentrations of isoflurane anesthesia than an ET.

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Total Intravenous Anesthesia: Effects of Opioid Versus Hypnotic Supplementation on Autonomic Responses and Recovery

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During radical prostatectomy procedures under total intravenous anesthesia, acute hemodynamic responses to retropubic dissection (30% ± 8% to 36% ± 12% [mean ± SD] increases in mean arterial pressure) were treated with supplemental doses of either an opioid analgesic (alfentanil) or a sedative-hypnotic (propofol) to return the mean arterial pressure to within 10% of the preincision value. Although both drugs were effective, control with propofol required 10.1 ± 2.5 min compared with 6.3 ± 2.6 min in the alfentanil group (mean ± SD; $P < 0.01$). Plasma stress hormone concentrations increased significantly in response to this surgical stimulus: epinephrine increased from 246% ± 169% to 283% ± 330%; norepinephrine increased from 44% ± 33% to 83% ± 104%; and antidiuretic hormone increased from 1300% ± 1591% to 1700% ± 1328%. Both alfentanil and propofol were equally effective in returning the catecholamine concentrations to their preincision levels. However, antidiuretic hormone levels remained above preincision values in both groups. Despite earlier awakening (3.4 ± 2.9 vs 9.1 ± 6.8 min; $P < 0.05$) in the alfentanil treatment group, there was no difference in time to spontaneous ventilation or tracheal extubation between the groups. In addition, 36% of the alfentanil-treated patients required antihypertensive therapy in the postanesthesia care unit compared with only 9% in the propofol group ($P < 0.05$). Postanesthesia care unit and hospital discharge times were similar in both treatment groups. We conclude that supplemental doses of alfentanil or propofol were equally effective in controlling acute hemodynamic and hormonal responses to surgical stimuli during total intravenous anesthesia.

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Total intravenous anesthesia (TIVA) involves the combined use of intravenous sedative-hypnotic, opioid analgesic, and muscle-relaxant drugs (1–4). Alfentanil and propofol are rapid, short-acting compounds with similar pharmacokinetic profiles. Although pharmacokinetic modeling suggests that sufentanil is an acceptable opioid analgesic to combine with propofol infusions during TIVA techniques lasting <6–8 h (5), most early studies involving TIVA techniques used concomitant infusions of alfentanil and propofol (6–9). While fixed-dosage regimens are frequently used, it is unclear whether it is preferable to vary the opioid analgesic or the sedative-hypnotic infusion to maintain hemodynamic stability during the intraoperative period.

Acute hemodynamic changes during nitrous oxide/opioid/relaxant ("balanced") anesthetic techniques are associated with increases in stress hormones (10,11). Marked elevations in heart rate (HR), mean arterial blood pressure (MAP), and catecholamine levels are stressful to patients with cardiac disease and have been associated with an increased incidence of postoperative renal and cardiac complications (12,13). Both alfentanil and isoflurane are equally effective in treating these acute autonomic responses (11). However, the optimal technique for treating acute hemodynamic and stress hormone responses during TIVA is unknown. Therefore, we designed a randomized, single-blind protocol to eval-

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uate the intraoperative hemodynamic and stress hormone responses during a standardized TIVA technique involving alfentanil, propofol, and vecuronium infusions. In addition, we compared the effectiveness of administering either supplemental analgesic (alfentanil) or hypnotic (propofol) medication to control acute autonomic responses during TIVA. Finally, we compared the effects of variable-rate alfentanil and propofol infusions on recovery profiles.

Methods

After approval of this study by the Washington University Human Studies Committee, 25 consenting adult men, ASA physical status I–III, scheduled to undergo elective radical prostatectomy procedures under general anesthesia were assigned to one of two anesthetic treatment groups according to a randomized, single-blind protocol in which the patient was unaware of the treatment group. Exclusionary criteria included history of allergic reaction to the study medications, long-term opioid or sedative use, obesity (>130% of ideal body weight), clinically significant hepatic or renal dysfunction, endocrine disease, and inadequately controlled chronic hypertension.

On arrival in the preoperative holding area, a peripheral venous catheter was inserted, and all patients received midazolam (2–4 mg IV). After placement of a radial artery catheter, patients were transported to the operating room, and preinduction (baseline) hemodynamic values were obtained. Anesthesia was induced with alfentanil (20 $\mu g/kg$), propofol (1.5 mg/kg IV), and vecuronium (0.1 mg/kg IV). After tracheal intubation, anesthesia was maintained with constant-rate infusions of alfentanil (0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$) and propofol (50 $\mu g \cdot kg^{-1} \cdot min^{-1}$). Neuromuscular blockade was maintained with a vecuronium infusion at 0.8 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Ventilation was controlled with 30% oxygen in air to maintain an end-tidal carbon dioxide tension (P_{ETCO_2}) of 34 ± 3 mm Hg (mean ± SD). Arterial blood samples were obtained 1–2 min before skin incision to determine Pa_{CO_2} (37 ± 5 mm Hg). The MAP and HR were continuously monitored using an integrated monitor (Cardiocap II, Datex Medical Instrumentation, Tewksbury, Mass.). Central venous pressure was monitored via a catheter placed in an internal jugular vein after tracheal intubation. The central venous pressure was maintained between 3 and 8 mm Hg throughout the study period by administering crystalloid and hetastarch (Hespan) or blood products.

Blood samples were obtained from the arterial catheter for determination of plasma catecholamines, vasopressin (antidiuretic hormone [ADH]), β-endorphin, cortisol, insulin, pancreatic polypeptide, and C-peptide concentrations at 1–2 min before skin incision (preincision) and 3–5 min after the onset of the hypertensive response during retropubic dissection (pretherapy). Plasma alfentanil and propofol concentrations were measured using arterial blood samples obtained at the same time intervals. Blood for catecholamine analysis was collected into tubes containing reduced glutathione and ethyleneglycol bis(aminoethylether)tetraacetate, and the blood samples for the remainder of the hormone assays were collected into ethylenediaminetetraacetate-containing tubes. These samples were immediately placed on ice and the plasma separated with a refrigerated centrifuge. All samples were stored at −70°C until the assays were performed.

Epinephrine and norepinephrine concentrations were determined using radioenzymatic assay techniques, with minimal assay sensitivities of 20 pg/mL and coefficients of variation of ±10%; all other hormone concentrations were determined using radioimmune assay techniques (14–17). The lower limits of sensitivity for the radioimmune assay were ADH (1 pg/mL), β-endorphin (8 pg/mL), cortisol (1 $\mu g/dL$), insulin (4 $\mu U/mL$), pancreatic polypeptide (20 pg/mL), and C-peptide (0.05 ng/mL). Plasma alfentanil concentrations were measured using a standardized radioimmunoassay with a lower limit of sensitivity of 5 ng/mL (18), and plasma propofol concentrations were measured using high-performance liquid chromatography by ICI Americas Inc. (Wilmington, Del.), with a lower limit of sensitivity of 50 ng/mL.

Patients exhibiting an increase in MAP of 25% or more above their preincision MAP for a minimum of 3 min were randomly treated using supplemental alfentanil or propofol to return the MAP to within 10% of the preincision value. In the alfentanil group, patients initially received a 10-$\mu g/kg$ bolus dose, and the infusion rate was increased by 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (with an additional bolus dose and increases in the infusion rate repeated every 2–3 min until the MAP decreased). In the propofol group, patients initially received a 0.3-mg/kg bolus dose, and the infusion rate was increased by 50 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (these supplemental dosages were repeated every 2–3 min until the MAP decreased). After maintaining a stable MAP for 10 min, repeat blood samples were obtained for determination of posttherapy hormone as well as analgesic and hypnotic drug concentrations. This sampling point was chosen because plasma catecholamines have a plasma half-life of <2 min, and this time interval allowed us to evaluate the effect of the treatment on the catecholamine stress response (10). In addition, secretion of stress hormones by the anterior pituitary occurs 5–10 min after the occurrence of an acute hypertensive event (19).

During the remainder of the operative period, the adjunctive therapy was adjusted to maintain hemodynamic stability in the two treatment groups. If the MAP remained within 10% of the preincision MAP for a period of 20–30 min, the alfentanil or propofol variable rate infusion was decreased by 50%. If the MAP remained stable, the adjunctive therapy was further decreased by 25% every 20–30 min until the minimal effective supplemental dose of the variable-rate alfentanil or propofol infusion was determined during the maintenance period. Adjunctive therapy was returned to the pretherapy baseline infusion rate if MAP decreased below the preincision value for >5 min.

On initiating skin closure, the vecuronium and alfentanil infusions were discontinued. At the end of surgery, residual neuromuscular blockade was reversed with neostigmine (0.07 mg/kg) and glycopyrrolate (0.01 mg/kg), and the propofol infusion was discontinued. The times from termination of the propofol infusion to spontaneous eye opening, purposeful response to verbal commands, adequate spontaneous ventilation, tracheal extubation, and orientation (to person, place, and time) were recorded. The recovery endpoints were evaluated at 5–10-s intervals after spontaneous eye opening. If adequate spontaneous ventilation did not occur within 10 min (with $P_{ET}CO_2$ ≥45 mm Hg), naloxone (0.04 mg IV) was administered every 60 s until spontaneous ventilation was adequate ($P_{ET}CO_2$ <50 mm Hg).

On arrival in the postanesthesia care unit (PACU), the patients were given 40% oxygen via face mask and observed by a nurse who was unaware of the treatment groups. If a patient complained of pain, morphine sulfate (1–2 mg IV) was administered at 2–5-min intervals until the patient was comfortable. Postoperative nausea or vomiting, or both, was treated with metoclopramide (10–20 mg IV). If the patients' postoperative MAP exceeded 25% of their preoperative baseline value for >5 min after achieving adequate pain control, labetalol (5–10 mg IV) or hydralazine (2.5–5 mg IV) was administered as needed to return the MAP value to within 10% of the preoperative baseline value. The dosage requirements for analgesic, antiemetic, and antihypertensive drugs in the PACU were recorded. Standardized PACU discharge criteria required that the patient be alert and oriented, have a stable MAP, HR, and respiratory rate, hemoglobin oxygen saturation >95%, and that residual side effects (e.g., nausea, pain) be minimal.

At the time of discharge from the PACU, patients were given a patient-controlled analgesia device (Baxter Infusor, Chicago, Ill.) that allowed them to self-administer morphine sulfate (2 mg [0.5 mL] IV) at minimal intervals of 6 min. All patients were visited daily to evaluate their overall recovery status and analgesia usage. On the fifth postoperative day, the patients completed a questionnaire with regard to their satisfaction with the anesthetic technique.

Table 1. Demographic Characteristics, Baseline Hemodynamic Values, and Plasma Drug Concentrations in the Two Treatment Groups

	Alfentanil (n = 11)	Propofol (n = 11)
Age (yr)	66 ± 6	67 ± 6
Weight (kg)	83 ± 11	83 ± 9
Height (cm)	177 ± 9	175 ± 5
Preexisting conditions		
Chronic hypertension	3	4
Coronary artery disease	2	3
β-Blocker therapy	2	3
Ca^+-channel blocker therapy	2	2
Mean arterial blood pressure (mm Hg)	105 ± 10	100 ± 11
Heart rate (beats/min)	70 ± 9	67 ± 11
Alfentanil concentration (ng/mL)		
Preincision	64 ± 15	79 ± 16
Pretherapy	67 ± 19	80 ± 14
Propofol concentration (μg/mL)		
Preincision	1.7 ± 1.0	1.9 ± 0.6
Pretherapy	1.5 ± 0.6	2.2 ± 1.9
Surgical time (min)	245 ± 22	225 ± 64

Values are mean ± SD, or numbers.

Data were analyzed using the STATA statistical analysis program, with one-way analysis of variance for continuous variables and the χ^2 test for discrete variables. Changes over time were evaluated using repeated measures of analysis of variance and Student's t-test, with a Bonferroni correction for multiple comparisons. Intergroup differences were evaluated using Tukey's post hoc test. Differences were considered to be statistically significant if the P value was <0.05. Values are expressed as mean ± SD (unless otherwise specified).

Results

Of the 25 study patients, 22 (88%) exhibited acute hypertensive responses on surgical entry into the retropubic space and were randomized to one of the two drug treatment groups. There were no differences in age, weight, height, and baseline hemodynamic values between the two study groups (Table 1). In addition, both groups had similar incidences of preexisting hypertension, coronary artery disease, and long-term usage of calcium-channel and β-adrenergic blocking drugs (Table 1).

Similar dosages of midazolam (2.6 ± 0.5 vs 2.6 ± 0.8 mg), alfentanil (1.6 ± 0.2 vs 1.7 ± 0.2 mg), propofol (122.7 ± 12.7 vs 125.1 ± 13.2 mg), and vecuronium (9.2 ± 1.0 vs 9.3 ± 1.0 mg) were administered during the induction period in the alfentanil and propofol treatment groups, respectively. Plasma

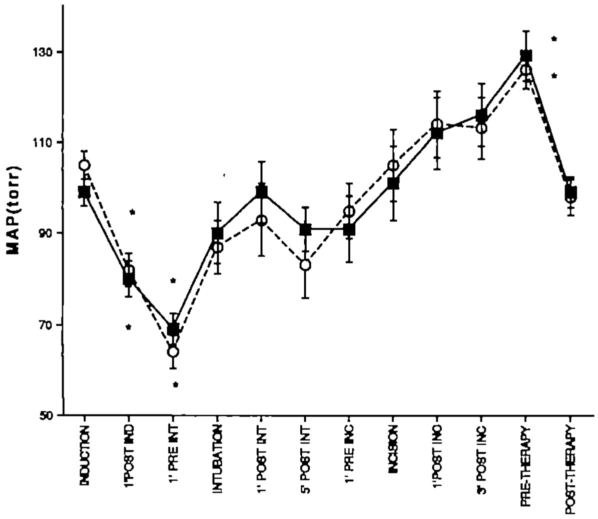

Figure 1. Intraoperative changes in mean arterial pressure (MAP) in patients receiving adjunctive therapy with either alfentanil (n = 11 [○]) or propofol (n = 11 [■]). Values are mean ± SEM. $^{*}P < 0.05$ was considered statistically significant when compared with induction (IND) (baseline) values. No differences were noted between the two treatment groups. INT, intubation; INC, incision.

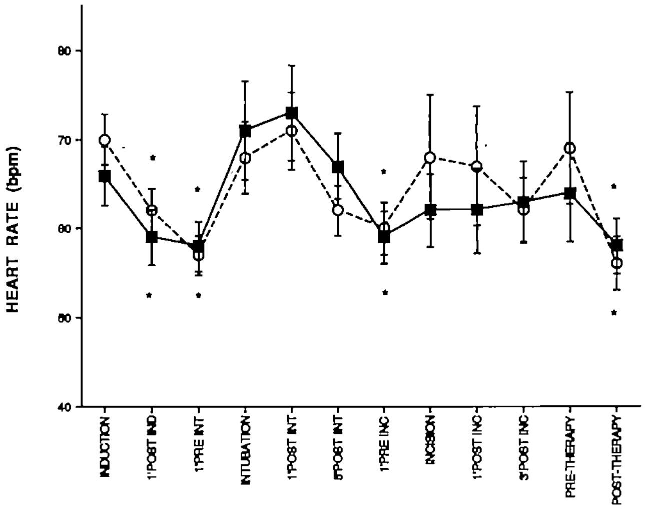

Figure 2. Intraoperative changes in heart rate (HR) in patients receiving adjunctive therapy with either alfentanil (n = 11 [○]) or propofol (n = 11 [■]). Values are mean ± SEM. $^{*}P < 0.05$ was considered statistically significant when compared with induction (IND) (baseline) values. No differences were noted between the two treatment groups. bpm, beats per minute; INT, intubation; INC, incision.

alfentanil and propofol concentrations were comparable in both groups at the preincision and pretherapy time intervals (Table 1). As expected, the posttherapy alfentanil concentration was significantly higher in the alfentanil-treated patients (162 ± 59 ng/mL) compared with the propofol group (93 ± 17 ng/mL). Conversely, the posttherapy propofol concentration was significantly higher in the propofol-treated patients (5.5 ± 2.7 μg/mL) than in the alfentanil group (1.4 ± 0.4 μg/mL). In the alfentanil group, the total alfentanil and propofol dosages were 25.6 ± 9.1 mg (range 15.0–46.8) and 1185 ± 161 mg (range 958–1424 mg), respectively. In the propofol group, the total alfentanil and propofol dosages were 10.5 ± 2.5 mg (range 6.0–13.7) and 1980 ± 774 mg (range 877–3049), respectively. The total vecuronium dosages in the alfentanil and propofol groups were similar (27.0 ± 5.0 mg [range 19–34] vs 24.5 ± 6.2 mg [range 11–30], respectively).

Perioperative changes in hemodynamic variables are summarized in Figures 1 and 2. Both groups had similar preinduction baseline MAP and HR values. After induction of anesthesia, there was a significant decrease in MAP and HR that persisted until the time of laryngoscopy in both groups. With tracheal intubation, MAP and HR returned to baseline values and remained stable until the surgeon entered the retropubic space (8.2 ± 7.8 and 8.6 ± 4.2 min after skin incision in the alfentanil and propofol groups, respectively). At that time, MAP values increased 30% ± 8% and 36% ± 12% in the two groups, respectively. However, HR values remained unchanged in both groups at the time of the acute hypertensive response. The time required for MAP values to return to within 10% of the preincision values was significantly shorter for alfentanil-treated patients (6.3 ± 2.6 min) compared with those receiving supplemental propofol (10.1 ± 2.5 min). Both groups experienced a significant decrease in HR after treatment of the acute hypertensive response. The MAP values were subsequently maintained within 10% of preincision values in both groups. Posttherapy stress hormone blood samples were obtained after maintaining a stable MAP for 10 min. There were no significant differences in MAP or HR values between the two treatment groups during the remainder of the surgical procedure.

All patients experienced significant increases in plasma epinephrine, norepinephrine, and ADH concentrations with the acute hypertensive response to retropubic dissection (Table 2). The plasma catecholamine concentrations returned to baseline values within 10 min after supplemental alfentanil or propofol treatment. Although the ADH levels decreased with both treatment modalities, the concentrations remained above baseline values. Although cortisol concentrations were unchanged immediately after the acute hypertensive response, they were significantly increased 10 min after "control" of the hypertensive response in both groups. Similarly, β-endorphin levels were significantly increased in both groups after treatment with either additional alfentanil or propofol. There were no changes in the plasma insulin, pancreatic polypeptide, or C-peptide

Table 2. Intraoperative Changes in Plasma Hormone Concentrations in the Two Treatment Groups

	Epinephrine (pg/mL)	Norepinephrine (pg/mL)	ADH (pg/mL)	Cortisol (μg/dL)	β-Endorphin (pg/mL)
Alfentanil group					
Preincision	44.5 ± 23.4	220.1 ± 106.8	2.5 ± 2.3	8.3 ± 2.8	24.0 ± 10.7
Pretherapy	122.9 ± 71.5^a	337.2 ± 94.3^a	24.7 ± 21.3^a	9.2 ± 4.3	28.6 ± 25.7
Posttherapy	51.6 ± 20.1	247.0 ± 75.4	14.8 ± 19.0	14.6 ± 6.8^a	33.0 ± 18.0^a
Propofol group					
Preincision	34.4 ± 17.1	225.2 ± 81.2	1.7 ± 0.5	6.4 ± 2.9	20.9 ± 8.8
Pretherapy	118.1 ± 80.5^a	329.1 ± 142.1^a	24.4 ± 30.0^a	6.2 ± 2.6	28.3 ± 11.2^a
Posttherapy	39.0 ± 28.1	219.2 ± 59.1	16.9 ± 29.7	12.1 ± 5.8^a	29.8 ± 13.3^a

Mean value ± SD.
[a]Significantly different from preincision values, $P < 0.05$.

Table 3. Postoperative Recovery Times (After Discontinuation of the Propofol Infusion) and Drug Treatment in the Postanesthesia Care Unit

	Alfentanil	Propofol
Awakening time (min)	3.4 ± 2.9	9.1 ± 6.8^a
Spontaneous ventilation time (min)	4.5 ± 3.5	5.6 ± 4.9
Tracheal extubation time (min)	8.9 ± 5.9	12.9 ± 9.7
Opioid antagonist (%)	27	18
Antihypertensive therapy (%)	36	9^a
Antiemetic therapy (%)	0	0
Morphine sulfate (mg)	4.2 ± 4.8	5.1 ± 5.9
PACU time (min)	114 ± 46	111 ± 42
Hospital discharge (days)	6.1 ± 0.4	6.1 ± 0.6

PACU, postanesthesia care unit.
Mean values ± SD.
[a]Significantly different from the alfentanil group, $P < 0.05$.

concentrations from their preincision values during he evaluation period (data not reported). No intergroup differences were found in any of the plasma hormone concentrations.

Similarly, there were no differences in the duration of surgery or times to resume spontaneous ventilaion or tracheal extubation after discontinuation of he propofol infusion between the two groups (Tables and 3). However, the time to awakening was ignificantly shorter in the alfentanil-treated patients. Although there was no difference in the requirement or opioid antagonism at the termination of the proedure, only 9% of the propofol-treated patients compared with 36% in the alfentanil group) required ntihypertensive therapy during their PACU stay. None of the patients in either group required antimetic therapy in the PACU. There was also no ifference in the duration of PACU stay or length of ospitalization between the two groups (Table 3). Postoperative opioid analgesic (morphine) requirements were similar in both TIVA treatment groups data not reported). The postoperative follow-up uestionnaire revealed that none of the patients exerienced recall of intraoperative events, and most of the patients were highly satisfied with their anesthetic technique (94%–97%).

Discussion

The alfentanil/propofol/vecuronium TIVA technique used in this study prevented clinical signs of inadequate anesthesia during skin incision in all patients; however, 88% of these patients experienced acute hypertensive responses and increases in stress hormone concentrations during retropubic dissection. The magnitude of the changes described during this operation were similar to the responses previously reported with a standardized nitrous oxide/opioid/muscle relaxant anesthetic technique (11). These observations are also in agreement with previous studies, indicating that skin incision was not the most intense stimulus during the intraoperative period (11,20).

In this patient population, a mean plasma alfentanil concentration of 70 (±17) ng/mL, in combination with a plasma propofol concentration of 1.8 (±1.0) μg/mL, was adequate to prevent clinical signs of inadequate anesthesia in response to skin incision. In previous studies utilizing balanced anesthesia with alfentanil, nitrous oxide, and a muscle relaxant, plasma alfentanil concentrations of 159–279 ng/mL were needed to prevent acute hemodynamic responses to skin incision (11,20). Analogous to the findings of Vuyk et al. (9), our data support the suggestion that the alfentanil requirement is decreased when administered with propofol during TIVA, compared with 67% nitrous oxide (as part of a "balanced" anesthetic technique) (11,20).

Other investigators have reported significant increases in plasma catecholamines, ADH, cortisol, and β-endorphin concentrations after acute hypertensive responses during general anesthesia with various combinations of intravenous and inhaled anesthetics (10,11,13,21–25). With the TIVA technique utilized in this study, we found significant increases in epinephrine, norepinephrine, and ADH concentrations within 5 min after the acute hypertensive response to retropubic dissection. Plasma cortisol and β-endorphin levels increased more slowly in both groups. The delayed elevation in plasma cortisol concentrations was not surprising, because changes in plasma cortisol concentration are mediated via adrenocorticotropic hormone and typically occur 5–15 min after the occurrence of a stressful event. Thus, the pretherapy sampling interval (3–5 min after the hypertensive response) was too short to reflect changes in this stress hormone. As reported previously during general anesthesia with volatile anesthetics (26,27), we found that gastrointestinal hormones (insulin, pancreatic polypeptide, C-peptide) were unchanged during retropubic dissection under TIVA.

Control of the acute hypertensive response to retropubic surgical dissection was achieved by administering additional alfentanil or propofol during TIVA. Although arterial blood pressure values returned to baseline more rapidly with alfentanil administration (6.3 ± 2.6 vs 10.1 ± 2.5 min for the propofol group), it is of limited (if any) clinical significance. Given the differing pharmacologic properties of alfentanil and propofol (i.e., opioid analgesic vs sedative-hypnotic), it is difficult to determine equipotent dosages for the two drugs. However, by increasing the size of the supplemental bolus dose of propofol, arterial blood pressure control could have been more rapidly achieved.

A recent study by Glass et al. (28) also evaluated the capacity of either supplemental opioid or hypnotic to control inadequate anesthesia during TIVA with fentanyl and propofol. They found more treatment "failures" in the fentanyl (vs propofol) treatment group. This apparent difference from our findings is probably related to the use of different opioids (alfentanil vs fentanyl) and dosage regimens (bolus dose plus an increase in the infusion rate vs an increase in the infusion rate alone) to control the acute autonomic signs of inadequate anesthesia.

During periods of surgical stress, stimulation of the sympathetic nervous system results in increased circulating levels of epinephrine and norepinephrine. If untreated, these levels may remain elevated throughout the procedure (29,30). In our study, treatment of the acute hypertensive response with either additional alfentanil or propofol resulted in a return of epinephrine and norepinephrine concentrations to their preincision values. These findings are in agreement with other studies, suggesting that supplemental opioid analgesic or anesthetic administration can block the sympathetic response to surgical stimulation (11,28,31–33). Increases in plasma cortisol and β-endorphin concentrations at the posttherapy sampling interval reflect the fact that β-endorphin and adrenocorticotropic hormone are secreted simultaneously from the anterior pituitary and that increases in plasma levels can peak as late as 15 min after a stressful event (19,34). However, there were no significant differences in neuroendocrine responses between the two treatment groups at any time during the study period.

Analogous to previous findings during balanced anesthesia (11), these findings suggest that the type of pharmacologic agent chosen to control acute hemodynamic responses during TIVA does not significantly affect the outcome after this major surgical procedure. Of note, the requirement for antihypertensive therapy in the PACU was significantly higher in the variable-rate alfentanil (vs propofol) infusion group. Because there were no differences in the postoperative analgesic requirements, a possible explanation relates to the residual cardiovascular depressant effects of propofol.

In achieving hemodynamic stability during TIVA, alfentanil and propofol were chosen because their relatively short durations of pharmacologic effects would minimize the possibility of prolonging the recovery period. These data support the suggestion that general anesthesia can be produced by using an hypnotic as the sole anesthetic agent. However, Glass et al. (28) found that the use of a fentanyl/propofol combination was associated with significantly shorter recovery times than propofol alone during TIVA. In using an opioid to treat signs of inadequate anesthesia during TIVA, it is important to ensure that the patient has an adequate level of hypnosis to prevent intraoperative recall. Adjunctive use of an amnestic premedicant (e.g., midazolam) will provide an additional "margin of safety" during TIVA.

In conclusion, hemodynamic and plasma hormone responses to noxious surgical stimuli during radical prostatectomy procedures under TIVA were similar to those reported during balanced anesthesia with nitrous oxide/alfentanil/muscle relaxant (11). Supplemental doses of alfentanil or propofol provided rapid control of both the acute hemodynamic and plasma hormone responses during TIVA with alfentanil, propofol, and vecuronium. Although emergence from TIVA was more rapid in alfentanil-supplemented patients, there were no significant differences in surgical outcome after this operation. During a TIVA technique with alfentanil and propofol, careful titration of either the opioid analgesic or the sedative-hypnotic will result in comparable intraoperative conditions and postoperative outcome. Further studies are needed to determine the optimal dosage regimens to maintain hemodynamic stability during TIVA.

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Defining the Dose Range for Esmolol Used in Electroconvulsive Therapy Hemodynamic Attenuation

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We evaluated the clinical effectiveness of esmolol, an ultra-short-acting, β-adrenergic receptor blocking drug, to control the sinus tachycardia and increase in arterial blood pressure induced by electroconvulsive therapy (ECT). Each of 20 patients, ASA physical status I–III, participated in a double-blind, randomized Latin-Square study involving two matched-pair trials (placebo versus esmolol given as a 500-μg/kg bolus followed by either 300 $\mu g \cdot kg^{-1} \cdot min^{-1}$ [high dose], 200 $\mu g \cdot kg^{-1} \cdot min^{-1}$ [medium dose], or 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$ [low dose] infusion of esmolol) during ECT. Each patient acted as his or her own control (total number of ECT procedures were 160). We administered a 1-min bolus of placebo (normal saline) or esmolol at the rate of 500 $\mu g \cdot kg^{-1} \cdot min^{-1}$ followed by either high-, medium-, or low-dose esmolol or placebo for an additional 3 min. We then induced anesthesia with methohexital (1 mg/kg) and succinylcholine (0.5 mg/kg) IV. Ninety seconds after the administration of succinylcholine, the electrical stimulus was applied to induce seizure. The infusion of placebo or esmolol was discontinued 3 min after the electrical stimulus. Significant decreases were found in mean heart rate from minute 3 until minute 7 and in the maximum heart rate. The mean of each patient's maximum heart rate after seizure changed from 147 ± 18 bpm in placebo patients to 112 ± 20 bpm in high-dose esmolol patients; to 121 ± 23 bpm in medium-dose esmolol patients; and to 124 ± 20 bpm in low-dose esmolol patients. Mean arterial blood pressure was significantly lower in the high-dose esmolol patients (100 ± 18 mm Hg) compared with the same patients given placebo (122 ± 25 mm Hg). Finally, the side effect of clinically determined length of seizures decreased in the high- (36 ± 14 s) and medium-dose (34 ± 14 s) esmolol patients as compared with placebo (42 ± 11 s) patients. Low-dose esmolol did not significantly reduce the clinically determined length of seizure (38 ± 11 s). We conclude that the 100-$\mu g \cdot kg^{-1} \cdot min^{-1}$ infusion following a 500-μg/kg bolus of esmolol effectively controls the hyperdynamic response to ECT.

(Anesth Analg 1992;75:805–10)

Electroconvulsive therapy (ECT) is used in the treatment of psychiatric illness, primarily major affective disorders, and certain cases of schizophrenia (1). This therapy works by electrically inducing grand mal seizures. Electroconvulsive therapy is known for its well-described, brief parasympathetic sequence followed by adrenergic outflow during the seizure, which markedly increases heart rate (HR) (2–6), arterial blood pressure (6,7), and plasma levels of catecholamines (8–10). These changes can produce cardiovascular stress in patients with heart disease.

This adrenergic response can be blunted effectively by premedication with clonidine or β-adrenergic blocking drugs (11,12). Of the β-blockers studied, esmolol seems uniquely suited to blocking the effects of adrenergic outflow during ECT based on its quick onset and short duration of action (13). A number of investigators have documented esmolol's ability to blunt the increases in HR and arterial blood pressure associated with ECT, using either a single bolus or an infusion at a variety of doses (6,11,14–17).

In a previous study (14), we noted that a large premedication dose of esmolol (2.9 mg/kg) for ECT decreased the duration of seizure by 27% as measured by electroencephalogram (EEG). Whether this effect is clinically relevant is not known (5,18), but it would be ideal to give the smallest dose of esmolol that would be clinically effective in blunting the adrenergic consequences of ECT to minimize any other potentially unwanted effects of the drug. A very low dose of esmolol (1-mg/kg bolus [6,16], 1.4-mg/kg bolus [17], or 1.5-mg/kg bolus [11]) does not influence duration of seizure. However, no es-

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molol dose-response study of hemodynamic response and seizure duration has been undertaken. This dose-response study investigates the effect of three different doses of esmolol premedication for ECT based on the hemodynamics and seizure duration in patients undergoing repetitive ECT treatments.

Methods

After approval by the Human Subjects Review Committee had been obtained, 20 consenting adult inpatients under the care of the Department of Psychiatry and scheduled for ECT were enrolled in the study. All patients were ASA class II–III. Exclusion criteria included pregnancy, age <21 yr, greater than first-degree atrioventricular block, allergy to β-adrenergic blockers, use of a β-blocker or calcium-channel blocker within four drug half-lives, atrial fibrillation or flutter, congestive heart failure, systolic blood pressure (SBP) consistently <100 mm Hg or diastolic blood pressure (DBP) <50 mm Hg, myocardial infarction within 6 mo, renal or hepatic failure, bronchospasm, or bronchial asthma.

Patients were entered into a randomized Latin-Square study so that every patient was placed twice into each of the four test groups: placebo control, high-dose esmolol, medium-dose esmolol, and low-dose esmolol. They were given no premedication before their arrival in the ECT suite. Patients were placed in a supine position, and a peripheral intravenous cannula infusing placebo (normal saline solution) or esmolol (high, medium, or low dose) was started. One author, not involved in the management of the patient, controlled the rate of infusion, which was hidden by a paper shroud from the view of others in the room. Patients were monitored with electrocardiography lead II, automated noninvasive blood pressure cuff, pulse oximetry, and EEG.

Anticholinergic premedication was not administered. After breathing oxygen, the patient received an infusion of either normal saline or esmolol. Those receiving esmolol were given 500 μg/kg over 1 min followed by 300 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (high dose), 200 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (medium dose), or 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (low dose). Four minutes after initiating the esmolol or placebo infusion, induction of anesthesia proceeded with 1 mg/kg methohexital. After loss of the eyelash reflex, 0.5 mg/kg succinylcholine was administered, followed 90 s later by the electrical stimulus to induce seizure. The esmolol or placebo infusion was discontinued 3 min after the electrical stimulus.

Heart rate, SBP, DBP, and mean blood pressure (MBP) were recorded at the following times: morning ward value, pretreatment baseline, every minute for 15 min after the initiation of esmolol or placebo infusion, and then every 5 min for an additional 20 min.

Statistical comparisons of the hemodynamic variables for the 160 trials from the 20 patients were performed using the one-way repeated measures analysis of variance tests with Duncan's multiple-range test to assess the significance of the results. The duration of the induced seizure as measured by the EEG and by clinical observation was recorded and compared between the study groups by the Kruskal-Wallis rank sum statistic.

Results

Each patient received an average of 12 ± 2 ECT treatments. Because all patients were entered twice in each of the four study groups, the mean demographics of the groups were identical: age 44 ± 18 yr, height 163 ± 18 cm, weight 64 ± 17 kg, and body surface area 1.68 ± 0.30 m^2. Hemodynamic variables (i.e., HR, SBP, DBP, and MBP) were equivalent during morning ward measurements and at baseline measurement in all four groups. There were no significant differences among shock stimulus variables used to induce seizure activity in any of the study groups (Table 1).

Patients given placebo manifested the expected significant increase in HR with seizure (Figure 1, minutes 6 and 7). In all three esmolol groups, HR was significantly decreased compared with placebo means (Figure 1, minute 3 until minute 7). This decrease was equivalent in all three esmolol groups. Maximal HR (the mean of each patient's maximal HR after seizure) changed from 147 ± 18 bpm in placebo patients to 112 ± 20 bpm in high-dose patients, to 121 ± 23 bpm in medium-dose patients, and to 124 ± 20 bpm in low-dose patients and was significantly ($P < 0.03$) more rapid in the placebo group when compared with baseline and with each esmolol group. There were no significant differences among the three esmolol study groups with respect to maximal HR.

Systolic blood pressure never changed from baseline after seizure in the three esmolol study groups; however, SBP increased significantly ($P < 0.05$) above baseline in the patients given placebo (Figure 2, minutes 7 and 8). Systolic blood pressure means from patients given placebo were significantly greater than SBP means from the three esmolol study groups at minutes 6, 7, and 8. There were no significant differences among the three esmolol study groups with respect to SBP. Diastolic blood pressure never changed from baseline after seizure in the patients given high-dose esmolol; however, DBP increased significantly from baseline at minute 7 in patients given placebo, medium-dose esmolol, and low-dose esmolol (Figure 3). In addition, the patients given placebo had significantly greater DBP at minute 7 than those patients given high-dose esmolol. There were no significant differences among the three es-

Table 1. Electroconvulsive Therapy in 20 Patients Given Infusion of Esmolol or Placebo[a]

Parameters	Placebo (n = 40)	Esmolol High dose (n = 40)	Esmolol Medium dose (n = 40)	Esmolol Low dose (n = 40)
Impedance (Ω)	197 ± 49	203 ± 46	202 ± 57	199 ± 48
Voltage (V)	139 ± 28	139 ± 29	134 ± 32	138 ± 25
Frequency (Hz)	71 ± 10	68 ± 9	69 ± 16	70 ± 12
Pulse width (μs)	1.6 ± 0.2	1.6 ± 0.2	1.6 ± 0.3	1.6 ± 0.2
Current (amp)	0.7 ± 0.04	0.7 ± 0.04	0.7 ± 0.05	0.7 ± 0.06
EEG seizure duration (s)	67 ± 29	56 ± 27	64 ± 36	62 ± 26
Clinical seizure duration (s)	42 ± 11	36 ± 14[b]	34 ± 14[b]	38 ± 11
Energy (J)	30 ± 19	25 ± 11	29 ± 18	30 ± 17

EEG, electroencephalogram.
Values are mean ± SD.
[a] Electroconvulsive stimulus was given to all patients using the same electroconvulsive therapy device, model SR, Mecta Corp., Portland, Ore.
[b] Statistically significant ($P < 0.05$) difference compared with placebo measurements.

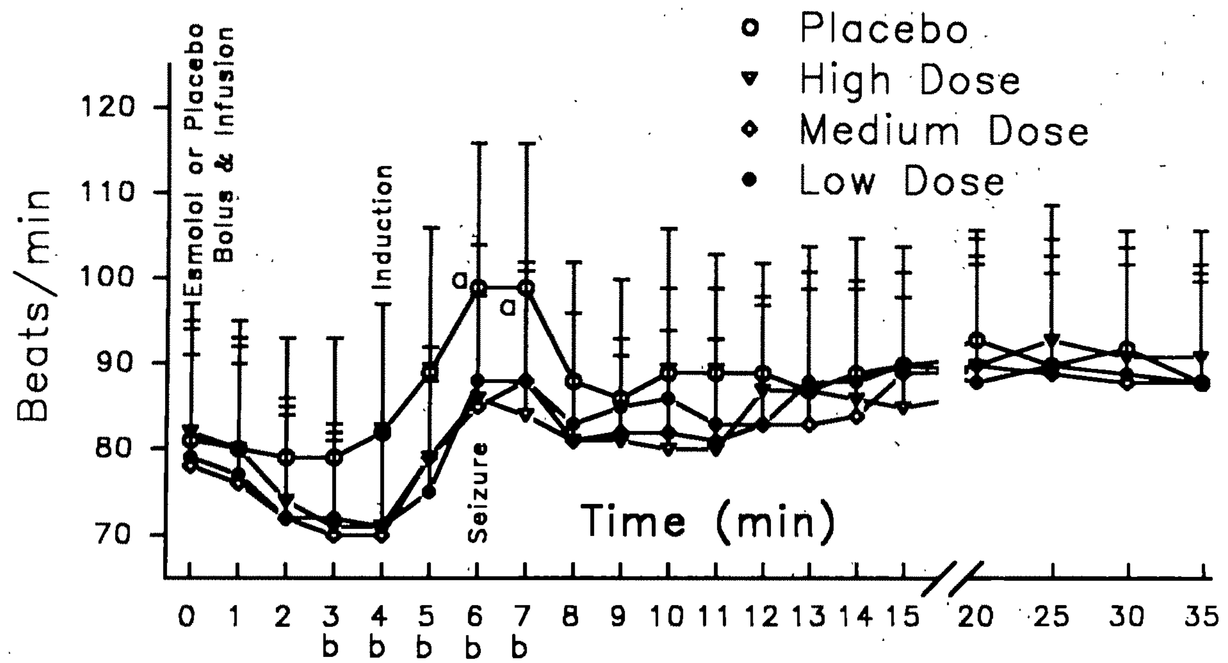

Figure 1. Mean values ± SD for heart rate (beats/min) for all 20 patients given either placebo or esmolol at high dose (300 $\mu g \cdot kg^{-1} \cdot min^{-1}$), medium dose (200 $\mu g \cdot kg^{-1} \cdot min^{-1}$), and low dose (100 $\mu g \cdot kg^{-1} \cdot min^{-1}$) during electroconvulsive therapy. [a] $P < 0.05$, significantly greater than placebo baseline. [b] $P < 0.05$, significantly less than placebo heart rate.

molol study groups with respect to DBP. Mean blood pressure never significantly changed from baseline after seizure in the three esmolol study groups; however, MBP increased significantly ($P < 0.05$) above baseline in the patients given placebo (Figure 4, minutes 7 and 8). There were no significant differences among the three esmolol study groups with respect to MBP.

No adverse events, such as bradycardia, hypotension, congestive heart failure, or bronchospasm, occurred in any of our study patients. Only the duration of seizure, as determined clinically, was statistically different between the placebo and medium- and high-dose esmolol groups, with seizure duration diminished in the latter two; however, there was no significant difference between the placebo and low-dose esmolol groups for the clinically determined duration of seizure (Table 1).

Discussion

These data demonstrate that an intravenous esmolol bolus of 500 μg/kg followed by an infusion of 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$ is as efficacious as larger doses in

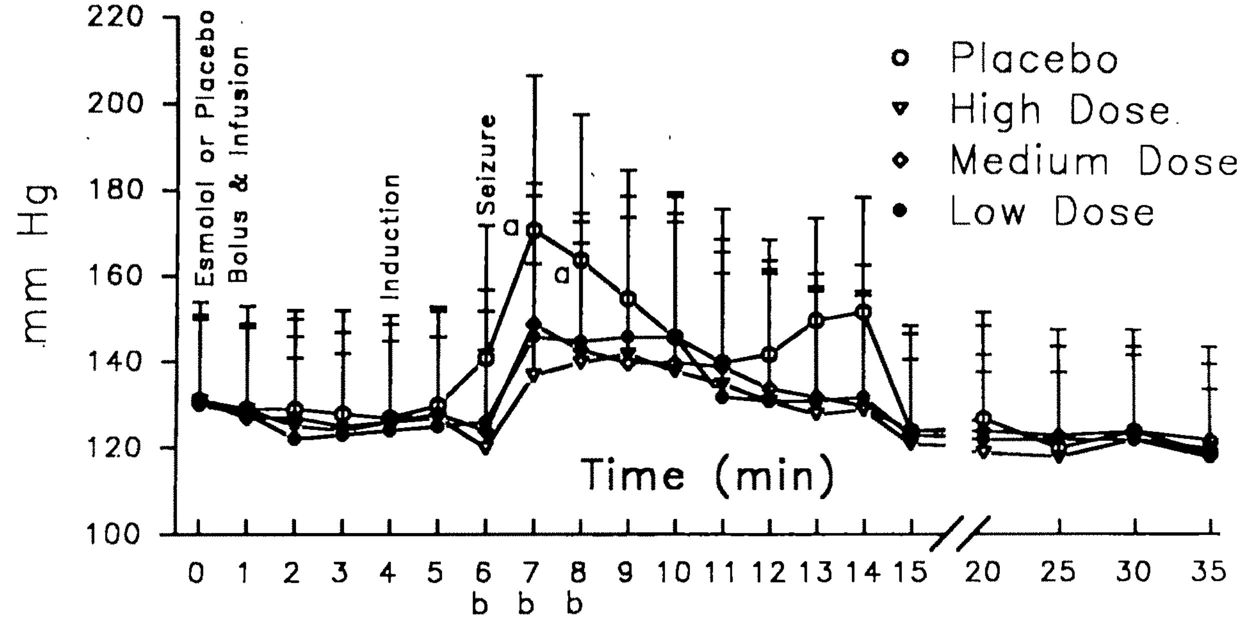

Figure 2. Mean values ± SD for systolic arterial blood pressure (mm Hg) for all 20 patients given either placebo or esmolol at high dose (300 μg·kg^{-1}·min^{-1}), medium dose (200 μg·kg^{-1}·min^{-1}), and low dose (100 μg·kg^{-1}·min^{-1}) during electroconvulsive therapy. $^{a}P < 0.05$, significantly greater than placebo baseline. $^{b}P < 0.05$, significantly less than placebo systolic blood pressure.

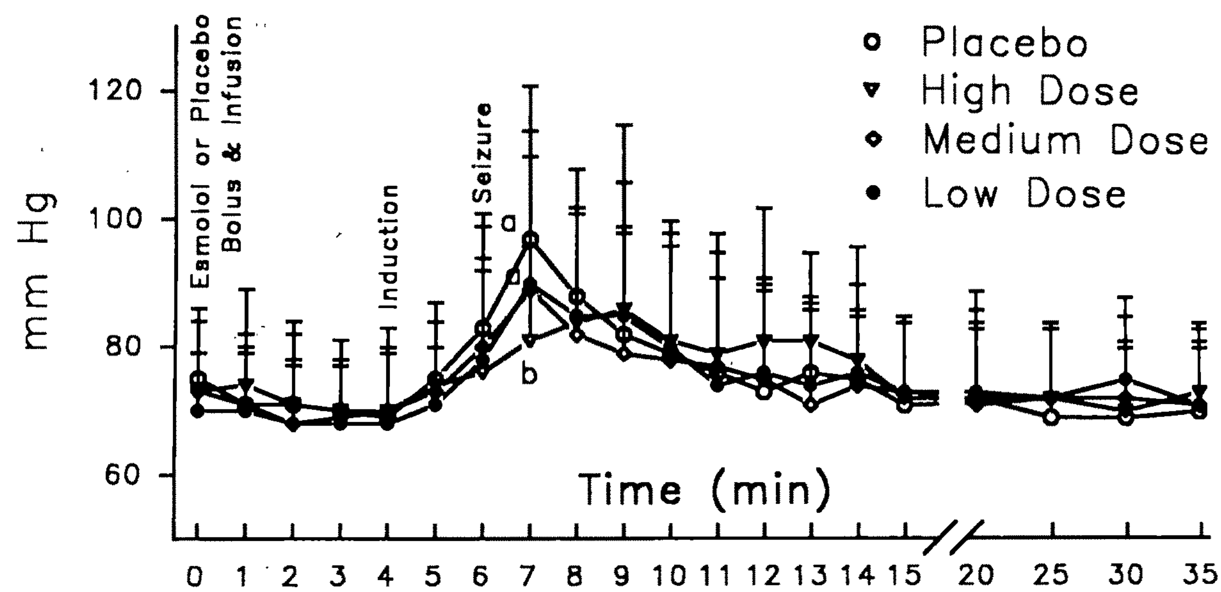

Figure 3. Mean values ± SD for diastolic arterial blood pressure (mm Hg) for all 20 patients given either placebo or esmolol at high dose (300 μg·kg^{-1}·min^{-1}), medium dose (200 μg·kg^{-1}·min^{-1}), and low dose (100 μg·kg^{-1}·min^{-1}) during electroconvulsive therapy. $^{a}P < 0.05$, significantly greater than their baseline. $^{b}P < 0.05$, significantly less than placebo diastolic blood pressure.

attenuating the hemodynamic changes of ECT when considering its effect on maximal HR and its ability to maintain arterial blood pressure at baseline levels. This dose does not appear to reduce the clinical or EEG-determined duration of seizure during ECT.

The effectiveness of premedication with β-adrenergic receptor blockers, especially esmolol, to attenuate the hemodynamic changes associated with ECT has been well documented. The application of any therapeutic technique in medicine requires careful evaluation of the benefits versus risks. As with any medical therapy, some effects are necessary for efficacy whereas others are superfluous.

Our placebo group yielded the characteristic pattern of ECT-associated hemodynamic changes: a marked tachycardia and increase in arterial blood

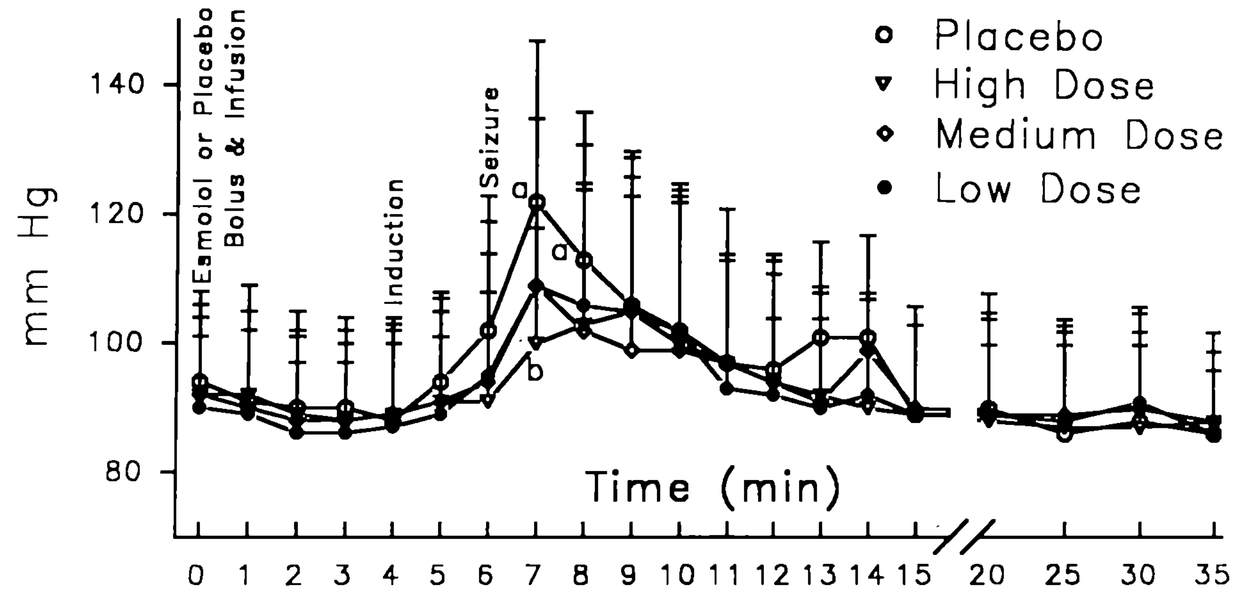

Figure 4. Mean values ± SD for mean arterial blood pressure (mm Hg) for all 20 patients given either placebo or esmolol at high dose (300 $\mu g \cdot kg^{-1} \cdot min^{-1}$), medium dose (200 $\mu g \cdot kg^{-1} \cdot min^{-1}$), and low dose (100 $\mu g \cdot kg^{-1} \cdot min^{-1}$) during electroconvulsive therapy. $^{a}P < 0.05$, significantly greater than placebo baseline. $^{b}P < 0.05$, significantly less than placebo mean blood pressure.

pressure beginning at seizure induction and persisting for several minutes. As was expected, in all three esmolol groups the HR decreased after the initiation of esmolol infusion until seizure initiation. After seizure initiation, however, the HR returned to baseline values and then remained there. There was no significant difference in HR among the low-dose, medium-dose, and high-dose esmolol groups.

Low-dose esmolol (i.e., a 500-μg/kg bolus dose followed by an infusion of 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was just as effective in attenuating the tachycardia and hypertension of ECT as a medium-range or high-range dose of esmolol (i.e., a 500-μg/kg bolus dose followed by an infusion of 200 $\mu g \cdot kg^{-1} \cdot min^{-1}$ or 300 $\mu g \cdot kg^{-1} \cdot min^{-1}$). In addition, there was a significant decrease in clinically observed seizure duration (8 s) between the placebo group and the medium-dose esmolol and high-dose esmolol groups, but no significant difference between the seizure duration in the placebo and low-dose esmolol groups. This is supported by others giving bolus doses of esmolol at 1 mg/kg (6,16), 1.4 mg/kg (17), or 1.5 mg/kg (11) without shortening duration of seizure, whereas a bolus of 2.86 mg/kg (17) and a bolus and infusion to a total of 2.9 mg/kg (14) did significantly shorten the duration of seizure. The only conflicting report was by Kovac et al. (15), where a bolus and infusion to a total of 3.88 mg/kg did not significantly shorten duration of seizure. However, Kovac premedicated placebo and esmolol patients with 0.3 mg of glycopyrrolate, which reduced the placebo patients' duration of EEG-measured seizure to only 45 s, making any shortening of seizure duration by esmolol difficult to detect. Whether duration of seizure is a significant determinant of the effectiveness of ECT remains unresolved. It is prudent, therefore, to use the lowest dose of esmolol that reliably attenuates the undesired hemodynamic effects of ECT. This study demonstrates that infusion of esmolol at 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$ after a bolus dose of 500 μg/kg is efficacious in blunting the hemodynamic response to ECT while not significantly changing the duration of the electrically induced seizure.

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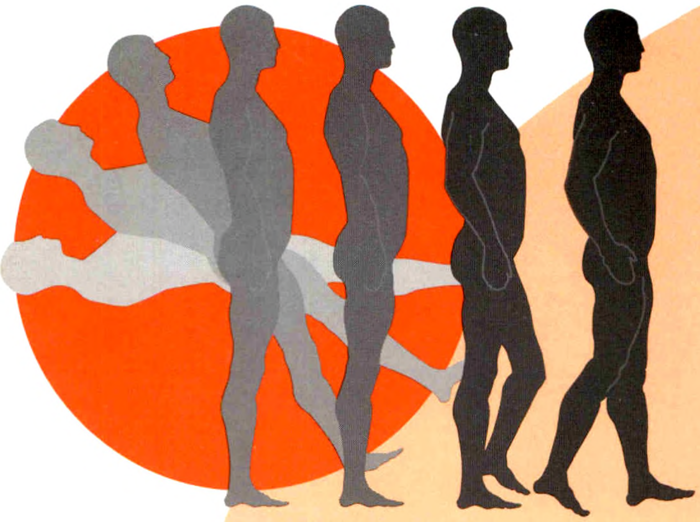

"The duration of action of mivacurium defines a new class of non-depolarizing neuromuscular blocking drugs."p.397

Caldwell JE, Heier T, Kitts JB, Lynam DP, Fahey MR, Miller RD. Comparison of the neuromuscular block induced by mivacurium, suxamethonium or atracurium during nitrous oxide-fentanyl anaesthesia. *Br J Anaesth*. 1989;63:393-399.

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Recommended initial adult dose

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Generally good to excellent intubating conditions

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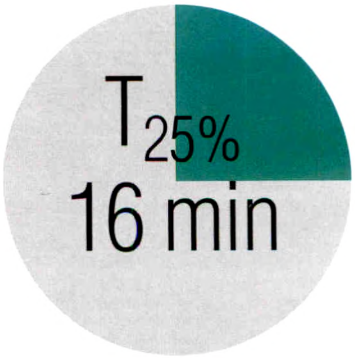

Short duration of action

Well-suited for short procedures

Duration of clinically effective block (time to 25% recovery of T_1) following injection of 0.15 mg/kg is 16 minutes, making **M**IVACRON excellent for short procedures.[1]

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Reduce spontaneous recovery time by up to 50% *vs* vecuronium

	Duration of continuous infusion (min)	Recovery times (min)		
		Off-25%*	25-75%	5-95%
MIVACRON (n=25)	**86.2±5.6**	**5.7±0.3**	**6.4±0.2**	**13.6±0.6**
vecuronium (n=18)	96.8±6.6	12.7±1.3†	13.8±0.9‡	32.0±1.2‡§
atracurium (n=22)	91.3±2.9	12.5±0.6†	10.9±0.3†	26.6±0.4†

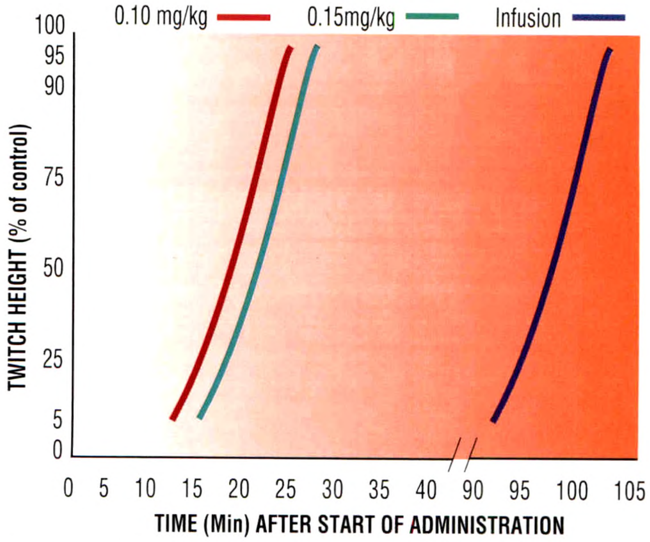
Adapted from Ali et al, p. 544.[2] *Time from discontinuation of infusion to 25% recovery. †P<0.01 atracurium or vecuronium vs **M**IVACRON; ‡P<0.001 vecuronium vs **M**IVACRON; §P<0.05 vecuronium vs atracurium.

Noncumulative

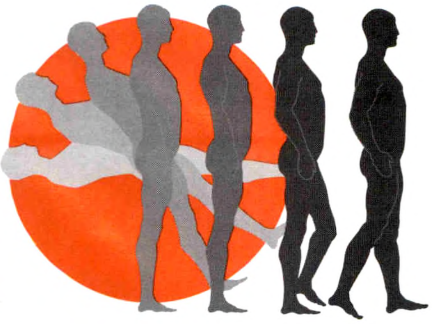
Continuous infusion of **M**IVACRON for up to 2.5 hours is not associated with the development of tachyphylaxis or cumulative neuromuscular blocking effects in ASA Physical Status I-II patients. Steady-state levels of block are rapidly achieved with minimal adjustment to the infusion rate. Limited data are available on **M**IVACRON (a mixture of three isomers) for infusions longer than 2.5 hours.

Savarese et al found...

Fast recovery following bolus or infusion



Adapted from Savarese et al, p. 727.[3]



MIVACRON® Injection 2 mg/mL

(mivacurium chloride)

Short duration, fast recovery

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MIVACRON®

Up to half the duration;

Excellent cardiovascular profile at recommended doses

MIVACRON Initial Dose* (mg/kg)	% of patients with ≥30% change			
	MAP		HR	
	↓	↑	↓	↑
0.07 to 0.10	0%	2%	0%	0%
0.15	4%	4%	4%	2%
0.20†	30%	0%	0%	8%
0.25†	39%	2%	0%	14%

*During opioid/N_2O/O_2 anesthesia.

†Experimental dose, in excess of the maximum recommended dose of 0.15 mg/kg.

Minimal CV effects

At the recommended initial dose of 0.15 mg/kg, cardiovascular response to **M**IVACRON is minimal. Higher doses may produce effects associated with histamine release and may result in a decrease in blood pressure in some individuals. The incidence and magnitude of these hemodynamic changes are related to size of the dose and speed of the injection. In patients with clinically significant CV disease, the initial dose of **M**IVACRON should be administered over 60 seconds.

Metabolized by plasma cholinesterase

Like succinylcholine, **M**IVACRON should be used with caution in patients with reduced plasma cholinesterase activity. In patients heterozygous for the atypical plasma cholinesterase gene, clinically effective duration may be prolonged by approximately 10 minutes. Homozygous patients (1 in 2500) are *extremely sensitive* to **M**IVACRON. **M**IVACRON should be used with great caution, if at all, in homozygous patients.

However, unlike succinylcholine, once recovery has begun, **M**IVACRON can be reversed with conventional doses of neostigmine.

Individualization of dosages

- Significant CV disease
- Obesity
- Renal or hepatic disease
- History suggesting greater sensitivity to release of histamine or related mediators

from Burroughs Wellcome Co.

ıalf the recovery time

nondepolarizing alternative to ıccinylcholine for elective ıtpatient surgery

	n	Time to max. block (min)*	Time to recovery of T_1=10% (min)*
ccinylcholine) mg/kg	9	1.1±0.2	7.7±1.4
IIVACRON 15 mg/kg	8	**2.5**±0.9	**15.6**±3.4

ıpted from Caldwell et al, p.395.[1] *P<0.05 succinylcholine vs **M**IVACRON.

ıldwell et al concluded...

> ..in those clinical situations in which ıpid onset of action is not required, ıivacurium is an alternative to [succinyl-ıoline] for production of profound neu-ımuscular block of short duration."p.398

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- For use by bolus or infusion
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- Available in 5 mL and 10 mL vials (2 mg/mL) and 50 mL premixed infusion bags (0.5 mg/mL)

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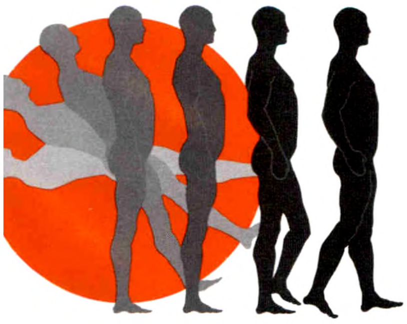

MIVACRON® Injection 2 mg/mL
(mivacurium chloride)
Short duration, fast recovery

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MIVACRON® INJECTION
MIVACRON® PREMIXED INFUSION
(MIVACURIUM CHLORIDE)

Brief Summary

This drug should be administered only by adequately trained individuals familiar with its actions, characteristics, and hazards.

INDICATIONS AND USAGE: MIVACRON is a short-acting neuromuscular blocking agent indicated for inpatients and outpatients, as an adjunct to general anesthesia, to facilitate tracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

CONTRAINDICATIONS: MIVACRON is contraindicated in patients known to have an allergic hypersensitivity to mivacurium chloride or other benzylisoquinolinium agents, as manifested by reactions such as urticaria or severe respiratory distress or hypotension. Use of MIVACRON from multi-dose vials is contraindicated in patients with a known allergy to benzyl alcohol.

WARNINGS: MIVACRON SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH THE DRUG'S ACTIONS AND THE POSSIBLE COMPLICATIONS OF ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS PERSONNEL AND FACILITIES FOR RESUSCITATION AND LIFE SUPPORT (TRACHEAL INTUBATION, ARTIFICIAL VENTILATION, OXYGEN THERAPY), AND AN ANTAGONIST OF MIVACRON ARE IMMEDIATELY AVAILABLE. IT IS RECOMMENDED THAT A PERIPHERAL NERVE STIMULATOR BE USED TO MEASURE NEUROMUSCULAR FUNCTION DURING THE ADMINISTRATION OF MIVACRON IN ORDER TO MONITOR DRUG EFFECT, DETERMINE THE NEED FOR ADDITIONAL DRUG, AND CONFIRM RECOVERY FROM NEUROMUSCULAR BLOCK.

MIVACRON HAS NO KNOWN EFFECT ON CONSCIOUSNESS, PAIN THRESHOLD, OR CEREBRATION. TO AVOID DISTRESS TO THE PATIENT, NEUROMUSCULAR BLOCK SHOULD NOT BE INDUCED BEFORE UNCONSCIOUSNESS.

MIVACRON IS METABOLIZED BY PLASMA CHOLINESTERASE AND SHOULD BE USED WITH GREAT CAUTION, IF AT ALL, IN PATIENTS KNOWN TO BE OR SUSPECTED OF BEING HOMOZYGOUS FOR THE ATYPICAL PLASMA CHOLINESTERASE GENE.

MIVACRON Injection and MIVACRON Premixed Infusion are acidic (pH 3.5 to 5.0) and may not be compatible with alkaline solutions having a pH greater than 8.5 (*e.g.*, barbiturate solutions).

PRECAUTIONS:

General: Although MIVACRON (a mixture of three stereoisomers) is not a potent histamine releaser, the possibility of substantial histamine release must be considered. Release of histamine is related to the dose and speed of injection.

Caution should be exercised in administering MIVACRON to patients with clinically significant cardiovascular disease and patients with any history suggesting a greater sensitivity to the release of histamine or related mediators (*e.g.*, asthma). In such patients, the initial dose of MIVACRON should be 0.15 mg/kg or less, administered over 60 seconds; assurance of adequate hydration and careful monitoring of hemodynamic status are important (see **Hemodynamics** and **Individualization of Dosages** subsections of CLINICAL PHARMACOLOGY).

Obese patients may be more likely to experience clinically significant transient decreases in MAP than non-obese patients when the dose of MIVACRON is based on actual rather than ideal body weight. Therefore, in obese patients, the initial dose should be determined using the patient's ideal body weight (see **Hemodynamics** and **Individualization of Dosages** subsections of CLINICAL PHARMACOLOGY).

Recommended doses of MIVACRON have no clinically significant effects on heart rate; therefore, MIVACRON will not counteract the bradycardia produced by many anesthetic agents or by vagal stimulation.

Neuromuscular blocking agents may have a profound effect in patients with neuromuscular diseases (*e.g.*, myasthenia gravis and the myasthenic syndrome). In these and other conditions in which prolonged neuromuscular block is a possibility (*e.g.*, carcinomatosis), the use of a peripheral nerve stimulator and a dose of not more than 0.015–0.020 mg/kg MIVACRON is recommended to assess the level of neuromuscular block and to monitor dosage requirements (see **Individualization of Dosages** subsection of CLINICAL PHARMACOLOGY).

MIVACRON has not been studied in patients with burns. Resistance to nondepolarizing neuromuscular blocking agents may develop in patients with burns, depending upon the time elapsed since the injury and the size of the burn. Patients with burns may have reduced plasma cholinesterase activity which may offset this resistance (see **Individualization of Dosages** subsection of CLINICAL PHARMACOLOGY).

Acid-base and/or serum electrolyte abnormalities may potentiate or antagonize the action of neuromuscular blocking agents. The action of neuromuscular blocking agents may be enhanced by magnesium salts administered for the management of toxemia of pregnancy (see **Individualization of Dosages** subsection of CLINICAL PHARMACOLOGY).

No data are available to support the use of MIVACRON by intramuscular injection.

Renal and Hepatic Disease: The possibility of prolonged neuromuscular block must be considered when MIVACRON is used in patients with renal or hepatic disease (see **Pharmacokinetics** subsection of CLINICAL PHARMACOLOGY). Most patients with chronic hepatic disease such as hepatitis, liver abscess, and cirrhosis of the liver exhibit a marked reduction in plasma cholinesterase activity. Patients with acute or chronic renal disease may also show a reduction in plasma cholinesterase activity (see **Individualization of Dosages** subsection of CLINICAL PHARMACOLOGY).

Reduced Plasma Cholinesterase Activity: The possibility of prolonged neuromuscular block following administration of MIVACRON must be considered in patients with reduced plasma cholinesterase (pseudocholinesterase) activity.

Plasma cholinesterase activity may be diminished in the presence of genetic abnormalities of plasma cholinesterase (*e.g.*, patients heterozygous or homozygous for the atypical plasma cholinesterase gene), pregnancy, liver or kidney disease, malignant tumors, infections, burns, anemia, decompensated heart disease, peptic ulcer, or myxedema. Plasma cholinesterase activity may also be diminished by chronic administration of oral contraceptives, glucocorticoids, or certain monoamine oxidase inhibitors and by irreversible inhibitors of plasma cholinesterase (*e.g.*, organophosphate insecticides, echothiophate, and certain antineoplastic drugs).

MIVACRON has been used safely in patients heterozygous for the atypical plasma cholinesterase gene. At doses of 0.10 to 0.20 mg/kg MIVACRON, the clinically effective duration of action was 8 to 11 minutes longer in patients heterozygous for the atypical gene than in genotypically normal patients.

As with succinylcholine, patients homozygous for the atypical plasma cholinesterase gene (1 in 2500 patients) are extremely sensitive to the neuromuscular blocking effect of MIVACRON. In three such adult patients, a small dose of 0.03 mg/kg (approximately the ED_{10-20} in genotypically normal patients) produced complete neuromuscular block for 26 to 128 minutes. Once spontaneous recovery had begun, neuromuscular block in these patients was antagonized with conventional doses of neostigmine. One adult patient, who was homozygous for the atypical plasma cholinesterase gene, received a dose of 0.18 mg/kg MIVACRON and exhibited complete neuromuscular block for about 4 hours. Response to post-tetanic stimulation was present after 4 hours, all four responses to train-of-four stimulation were present after 6 hours, and the patient was extubated after 8 hours. Reversal was not attempted in this patient.

Malignant Hyperthermia (MH): In a study of MH-susceptible pigs, MIVACRON did not trigger MH. MIVACRON has not been studied in MH-susceptible patients. Because MH can develop in the absence of established triggering agents, the clinician should be prepared to recognize and treat MH in any patient undergoing general anesthesia.

Long-Term Use in the Intensive Care Unit (ICU): No data are available on the long-term use of MIVACRON in patients undergoing mechanical ventilation in the ICU.

Drug Interactions: Although MIVACRON (a mixture of three stereoisomers) has been administered safely following succinylcholine-facilitated tracheal intubation, the interaction between the stereoisomers in MIVACRON and succinylcholine has not been systematically studied. Prior administration of succinylcholine can potentiate the neuromuscular blocking effects of nondepolarizing agents. Evidence of spontaneous recovery from succinylcholine should be observed before the administration of MIVACRON.

The use of MIVACRON before succinylcholine to attenuate some of the side effects of succinylcholine has not been studied.

There are no clinical data on the use of MIVACRON with other nondepolarizing neuromuscular blocking agents.

Isoflurane and enflurane (administered with nitrous oxide/oxygen to achieve 1.25 MAC) decrease the ED_{50} of MIVACRON by as much as 25% (see **Pharmacodynamics** and **Individualization of Dosages** subsections of CLINICAL PHARMACOLOGY). These agents may also prolong the clinically effective duration of action and decrease the average infusion requirement of MIVACRON by as much as 35% to 40%. A greater potentiation of the neuromuscular blocking effects of the stereoisomers in MIVACRON may be expected with higher concentrations of enflurane or isoflurane. Halothane has little or no effect on the ED_{50}, but may prolong the duration of action and decrease the average infusion requirement by as much as 20%.

Other drugs which may enhance the neuromuscular blocking action of nondepolarizing agents such as the stereoisomers in MIVACRON include certain antibiotics (*e.g.*, aminoglycosides, tetracyclines, bacitracin, polymyxins, lincomycin, clindamycin, colistin, and sodium colistimethate), magnesium salts, lithium, local anesthetics, procainamide, and quinidine. Drugs that may enhance the neuromuscular blocking effects of mivacurium by a reduction in plasma cholinesterase activity include chronic administration of oral contraceptives, glucocorticoids, or certain monoamine oxidase inhibitors and by irreversible inhibitors of plasma cholinesterase (see **Reduced Plasma Cholinesterase Activity** subsection of PRECAUTIONS).

Resistance to the neuromuscular blocking action of nondepolarizing neuromuscular blocking agents has been demonstrated in patients chronically administered phenytoin or carbamazepine. While the effects of chronic phenytoin or carbamazepine therapy on the action of the stereoisomers in MIVACRON are unknown, slightly shorter durations of neuromuscular block may be anticipated and infusion rate requirements may be higher.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis and fertility studies have not been performed. MIVACRON was evaluated in a battery of four short-term mutagenicity tests. It was non-mutagenic in the Ames Salmonella assay, the mouse lymphoma assay, the human lymphocyte assay, and the *in vivo* rat bone marrow cytogenetic assay.

Pregnancy: *Teratogenic Effects*: Pregnancy Category C. Teratology testing in nonventilated pregnant rats and mice treated subcutaneously with maximum subparalyzing doses of MIVACRON revealed no maternal or fetal toxicity or teratogenic effects. There are no adequate and well-controlled studies of MIVACRON in pregnant women. Because animal studies are not always predictive of human response, and the doses used were subparalyzing, MIVACRON should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: The use of MIVACRON during labor, vaginal delivery, or cesarean section has not been studied in humans and it is not known whether MIVACRON administered to the mother has effects on the fetus. Doses of 0.08 and 0.20 mg/kg MIVACRON given to female beagles undergoing cesarean section resulted in negligible levels of the stereoisomers in MIVACRON in umbilical vessel blood of neonates and no deleterious effects on the puppies.

Nursing Mothers: It is not known whether any of the stereoisomers of mivacurium are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised following administration of MIVACRON to a nursing woman.

Pediatric Use: MIVACRON has not been studied in children below the age of 2 years (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION for clinical experience and recommendations for use in children 2 to 12 years of age).

Geriatric Use: MIVACRON was safely administered during clinical trials to 64 elderly (≥65 years) patients, including 31 patients with significant cardiovascular disease (see **General** subsection of PRECAUTIONS). The duration of neuromuscular block may be slightly longer in elderly patients than in young adult patients (see CLINICAL PHARMACOLOGY).

ADVERSE REACTIONS:

Observed in Clinical Trials: MIVACRON (a mixture of three stereoisomers) was well tolerated during extensive clinical trials in inpatients and outpatients. Prolonged neuromuscular block, which is an important adverse experience associated with neuromuscular blocking agents as a class, was reported as an adverse experience in 3 of 2074 patients administered MIVACRON. The most commonly reported adverse experience following the administration of MIVACRON was transient, dose-dependent cutaneous flushing about the face, neck, and/or chest. Flushing was most frequently noted after the initial dose of MIVACRON and was reported in about 20% of adult patients who received the recommended dose of 0.15 mg/kg MIVACRON over 5 to 15 seconds. When present, flushing typically began within 1 to 2 minutes after the dose of MIVACRON and lasted for 3 to 5 minutes. Of 60 patients who experienced flushing after 0.15 mg/kg MIVACRON, one patient also experienced mild hypotension that was not treated, and one patient experienced moderate wheezing that was successfully treated.

Overall, hypotension was infrequently reported as an adverse experience in the clinical trials of MIVACRON. None of the 397 adults or 63 children who received recommended doses was treated for a decrease in blood pressure associated with the administration of MIVACRON. Above the recommended dosage range, 1% to 2% of healthy adults given ≥0.20 mg/kg over 5 to 15 seconds and 2% to 4% of cardiac surgery patients given ≥0.20 mg/kg over 60 seconds were treated for decreases in blood pressure associated with the administration of MIVACRON.

The following adverse experiences were reported in patients administered MIVACRON (all events judged by investigators during the clinical trials to have a possible causal relationship):

Incidence Greater Than 1% -

Cardiovascular:	Flushing (15%)

Incidence Less Than 1% -

Cardiovascular:	Hypotension, Tachycardia, Bradycardia, Cardiac Arrhythmia, Phlebitis
Respiratory:	Bronchospasm, Wheezing, Hypoxemia
Dermatological:	Rash, Urticaria, Erythema, Injection Site Reaction
Nonspecific:	Prolonged Drug Effect
Neurologic:	Dizziness
Musculoskeletal:	Muscle Spasms

OVERDOSAGE: Overdosage with neuromuscular blocking agents may result in neuromuscular block beyond the time needed for surgery and anesthesia. The primary treatment is maintenance of a patent airway and controlled ventilation until recovery of normal neuromuscular function is assured. Once evidence of recovery from neuromuscular block is observed, further recovery may be facilitated by administration of an anticholinesterase agent (*e.g.*, neostigmine, edrophonium) in conjunction with an appropriate anticholinergic agent. (see **Antagonism of Neuromuscular Block**). Overdosage may increase the risk of hemodynamic side effects, especially decreases in blood pressure. If needed, cardiovascular support may be provided by proper positioning of the patient, fluid administration, and/or vasopressor agent administration.

Antagonism of Neuromuscular Block:

ANTAGONISTS (SUCH AS NEOSTIGMINE) SHOULD NOT BE ADMINISTERED WHEN COMPLETE NEUROMUSCULAR BLOCK IS EVIDENT OR SUSPECTED. THE USE OF A PERIPHERAL NERVE STIMULATOR TO EVALUATE RECOVERY AND ANTAGONISM OF NEUROMUSCULAR BLOCK IS RECOMMENDED.

Administration of 0.030 to 0.064 mg/kg neostigmine or 0.5 mg/kg edrophonium at approximately 10% recovery from neuromuscular block (range: 1 to 15) produced 95% recovery of the muscle twitch response and a T_4/T_1 ratio ≥75% in about 10 minutes. The times from 25% recovery of the muscle twitch response to T_4/T_1 ratio ≥75% following these doses of antagonists averaged about 7 to 9 minutes. In comparison, average times for spontaneous recovery from 25% to T_4/T_1 ≥75% were 12 to 13 minutes.

Patients administered antagonists should be evaluated for adequate clinical evidence of antagonism, *e.g.*, 5-second head lift and grip strength. Ventilation must be supported until no longer required.

Antagonism may be delayed in the presence of debilitation, carcinomatosis, and the concomitant use of certain broad spectrum antibiotics, or anesthetic agents and other drugs which enhance neuromuscular block or separately cause respiratory depression (see **Drug Interactions** subsection of PRECAUTIONS). Under such circumstances the management is the same as that of prolonged neuromuscular block (see OVERDOSAGE).

DOSAGE AND ADMINISTRATION: MIVACRON SHOULD ONLY BE ADMINISTERED INTRAVENOUSLY.

The dosage information provided below is intended as a guide only. Doses of MIVACRON should be individualized (see **Individualization of Dosages** subsection of CLINICAL PHARMACOLOGY). Factors that may warrant dosage adjustment include but may not be limited to: the presence of significant kidney, liver, or cardiovascular disease, obesity (patients weighing ≥30% more than ideal body weight for height), asthma, reduction in plasma cholinesterase activity, and the presence of inhalational anesthetic agents. The use of a peripheral nerve stimulator will permit the most advantageous use of MIVACRON, minimize the possibility of overdosage or underdosage, and assist in the evaluation of recovery.

Adults:

Initial Doses:

A dose of 0.15 mg/kg MIVACRON administered over 5 to 15 seconds is recommended for facilitation of tracheal intubation for most patients. When administered as a component of a thiopental/opioid/nitrous oxide/oxygen induction-intubation technique, 0.15 mg/kg (2 x ED_{95}) MIVACRON produces generally good-to-excellent conditions for tracheal intubation in 2.5 minutes. Lower doses of MIVACRON may result in a longer time for development of satisfactory intubation conditions. Administration of MIVACRON doses above the recommended range (≥0.20 mg/kg) is associated with the development of transient decreases in blood pressure in some patients (see CLINICAL PHARMACOLOGY and ADVERSE REACTIONS).

STORAGE: Store MIVACRON Injection at room temperature of 15° to 25°C (59° to 77°F). Avoid exposure to direct ultraviolet light. DO NOT FREEZE.

Recommended storage for MIVACRON Premixed Infusion is room temperature (15° to 25°C/59° to 77°F). Avoid excessive heat. Avoid exposure to direct ultraviolet light. Protect from freezing.

U.S. Patent No. 4761418

BURROUGHS WELLCOME CO.
Research Triangle Park, NC 27709

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Manufactured for
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by Abbott Laboratories
North Chicago, IL 60064

06-4814
Printed in U.S.A. January 1992 670002

TRACRIUM® INJECTION

(atracurium besylate)

Brief Summary

This drug should be used only by adequately trained individuals familiar with its actions, characteristics, and hazards.

INDICATIONS AND USAGE: Tracrium is indicated, as an adjunct to general anesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

CONTRAINDICATIONS: Tracrium is contraindicated in patients known to have a hypersensitivity to it.

WARNINGS: TRACRIUM SHOULD BE USED ONLY BY THOSE SKILLED IN AIRWAY MANAGEMENT AND RESPIRATORY SUPPORT. EQUIPMENT AND PERSONNEL MUST BE IMMEDIATELY AVAILABLE FOR ENDOTRACHEAL INTUBATION AND SUPPORT OF VENTILATION, INCLUDING ADMINISTRATION OF POSITIVE PRESSURE OXYGEN. ADEQUACY OF RESPIRATION MUST BE ASSURED THROUGH ASSISTED OR CONTROLLED VENTILATION. ANTICHOLINESTERASE REVERSAL AGENTS SHOULD BE IMMEDIATELY AVAILABLE. DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION. Tracrium has no known effect on consciousness, pain threshold, or cerebration. It should be used only with adequate anesthesia. Tracrium Injection, which has an acid pH, should not be mixed with alkaline solutions (e.g., barbiturate solutions) in the same syringe or administered simultaneously during intravenous infusion through the same needle. Depending on the resultant pH of such mixtures, Tracrium may be inactivated and a free acid may be precipitated. Tracrium Injection 10 mL multiple dose vials contain benzyl alcohol. Benzyl alcohol has been associated with an increased incidence of neurological and other complications in newborn infants which are sometimes fatal. Tracrium Injection 5 mL single use vials do not contain benzyl alcohol.

PRECAUTIONS: General: Although Tracrium is a less potent histamine releaser than d-tubocurarine or metocurine, the possibility of substantial histamine release in sensitive individuals must be considered. Special caution should be exercised in administering Tracrium to patients in whom substantial histamine release would be especially hazardous (e.g., patients with clinically significant cardiovascular disease) and in patients with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release. In these patients, the recommended initial Tracrium dose is lower (0.3 to 0.4 mg/kg) than for other patients and should be administered slowly or in divided doses over one minute. Since Tracrium has no clinically significant effects on heart rate in the recommended dosage range, it will not counteract the bradycardia produced by many anesthetic agents or vagal stimulation. As a result, bradycardia during anesthesia may be more common with Tracrium than with other muscle relaxants. Tracrium may have profound effects in patients with myasthenia gravis, Eaton-Lambert syndrome, or other neuromuscular diseases in which potentiation of nondepolarizing agents has been noted. The use of a peripheral nerve stimulator is especially important for assessing neuromuscular blockade in these patients. Similar precautions should be taken in patients with severe electrolyte disorders or carcinomatosis. Multiple factors in anesthesia practice are suspected of triggering malignant hyperthermia (MH), a potentially fatal hypermetabolic state of skeletal muscle. Halogenated anesthetic agents and succinylcholine are recognized as the principal pharmacologic triggering agents in MH-susceptible patients; however, since MH can develop in the absence of established triggering agents, the clinician should be prepared to recognize and treat MH in any patient scheduled for general anesthesia. Reports of MH have been rare in cases in which Tracrium has been used. In studies of MH-susceptible animals (swine) and in a clinical study of MH-susceptible patients, Tracrium did not trigger this syndrome. Resistance to nondepolarizing neuromuscular blocking agents may develop in burn patients. Increased doses of nondepolarizing muscle relaxants may be required in burn patients and are dependent on the time elapsed since the burn injury and the size of the burn. The safety of Tracrium has not been established in patients with bronchial asthma. **Long-Term Use in Intensive Care Unit (ICU):** Tracrium has been used to facilitate mechanical ventilation in ICU patients. When there is a need for long-term mechanical ventilation, the benefits to risk ratio of neuromuscular blockade must be considered. There is only limited information on the efficacy and safety of Tracrium administered by long-term (days to weeks) intravenous infusion to facilitate mechanical ventilation in intensive care facilities. For Tracrium, as with other neuromuscular blocking agents used in intensive care facilities, available evidence suggests that there is wide interpatient variability in dosage requirements and that these requirements may change with time. Limited data suggest that Tracrium infusion requirements may increase with prolonged administration in the ICU. As with other neuromuscular blocking agents, little information is available on the plasma levels or clinical consequences of atracurium metabolites following long-term (days to weeks) infusion of Tracrium in the intensive care unit setting. One metabolite of atracurium, laudanosine, when administered alone to laboratory animals, has been associated with cerebral excitatory effects. Physiological effects of laudanosine in humans have not been demonstrated. The effects of hemodialysis, hemoperfusion and hemofiltration on plasma levels of atracurium and its metabolites are unknown. **Drug Interactions:** Drugs which may enhance neuromuscular blocking action of Tracrium include: enflurane; isoflurane; halothane; certain antibiotics, especially the aminoglycosides and polymyxins; lithium; magnesium salts; procainamide; and quinidine. If other muscle relaxants are used during the same procedure, the possibility of a synergistic or antagonist effect should be considered. The prior administration of succinylcholine does not enhance the duration, but quickens the onset and may increase the depth, of neuromuscular blockade induced by Tracrium. Tracrium should not be administered until a patient has recovered from succinylcholine-induced neuromuscular blockade. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** A positive response was observed in the mouse lymphoma assay under conditions which killed over 80% of the treated cells. A far weaker response was observed in the presence of metabolic activation at concentrations which also killed over 80% of the treated cells. **Pregnancy: *Teratogenic Effects:*** Pregnancy Category C. Tracrium has been shown to be potentially teratogenic in rabbits, when given in doses up to approximately one-half the human dose. There are no adequate and well-controlled studies in pregnant women. Tracrium should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Labor and Delivery:** It is not known whether muscle relaxants administered during vaginal delivery have immediate or delayed adverse effects on the fetus or increase the likelihood that resuscitation of the newborn will be necessary. The possibility that forceps delivery will be necessary may increase. Tracrium (0.3 mg/kg) has been administered to 26 pregnant women during delivery by cesarean section. No harmful effects were attributable to Tracrium in any of the newborn infants, although small amounts of Tracrium were shown to cross the placental barrier. The possibility of respiratory depression in the newborn infant should always be considered following cesarean section during which a neuromuscular blocking agent has been administered. In patients receiving magnesium sulfate, the reversal of neuromuscular blockade may be unsatisfactory and Tracrium dose should be lowered as indicated. **Nursing Mothers:** It is not known whether this drug is excreted in human milk. Caution should be exercised when Tracrium is administered to a nursing woman. **Pediatric Use:** Safety and effectiveness in children below the age of 1 month have not been established.

ADVERSE REACTIONS: Observed in Controlled Clinical Studies: Tracrium produced few adverse reactions during extensive clinical trials. Most were suggestive of histamine release (see Precautions Section). The overall incidence rate for clinically important adverse reactions was 7/875 or 0.8%. Most adverse reactions were of little clinical significance unless they were associated with significant hemodynamic changes. Substantial vital sign changes greater than or equal to 30% observed in 530 patients, without cardiovascular disease, were as follows: In those patients given the recommended initial dosage range of 0.31 to 0.50 mg/kg of Tracrium, mean arterial pressure increased in 2.8% and decreased in 2.1% of patients while the heart rate increased in 2.8% of these patients. At doses of ≥ 0.60 mg/kg, 14.3% of the studied patients had a decrease in mean arterial pressure while 4.8% had an increase in heart rate. At doses ≤ 0.30 mg/kg, mean arterial pressure increased in 1.9% and decreased in 1.1% of patients, while heart rate increased in 1.6% and decreased in 0.8% of these patients. **Observed in Clinical Practice:** Based on clinical experience in the U.S. and the United Kingdom of approximately 3 million patients given Tracrium the following adverse reactions are among the most frequently reported: *General:* allergic reactions (anaphylactic or anaphylactoid) which, in rare instances, were severe (e.g., cardiac arrest); *Musculoskeletal:* inadequate, prolonged block; *Cardiovascular:* hypotension, vasodilatation (flushing), tachycardia, bradycardia; *Respiratory:* dyspnea, bronchospasm, laryngospasm; *Integumentary:* rash, urticaria, injection site reaction.

STORAGE: Tracrium Injection should be refrigerated at 2° to 8° C (36° to 46° F) to preserve potency. DO NOT FREEZE. Upon removal from refrigeration to room temperature storage conditions (25°C/77°F), use Tracrium Injection within 14 days even if rerefrigerated.

U.S. Patent No. 4179507 December 1990 627248

Burroughs Wellcome Co., Research Triangle Park, North Carolina 27709

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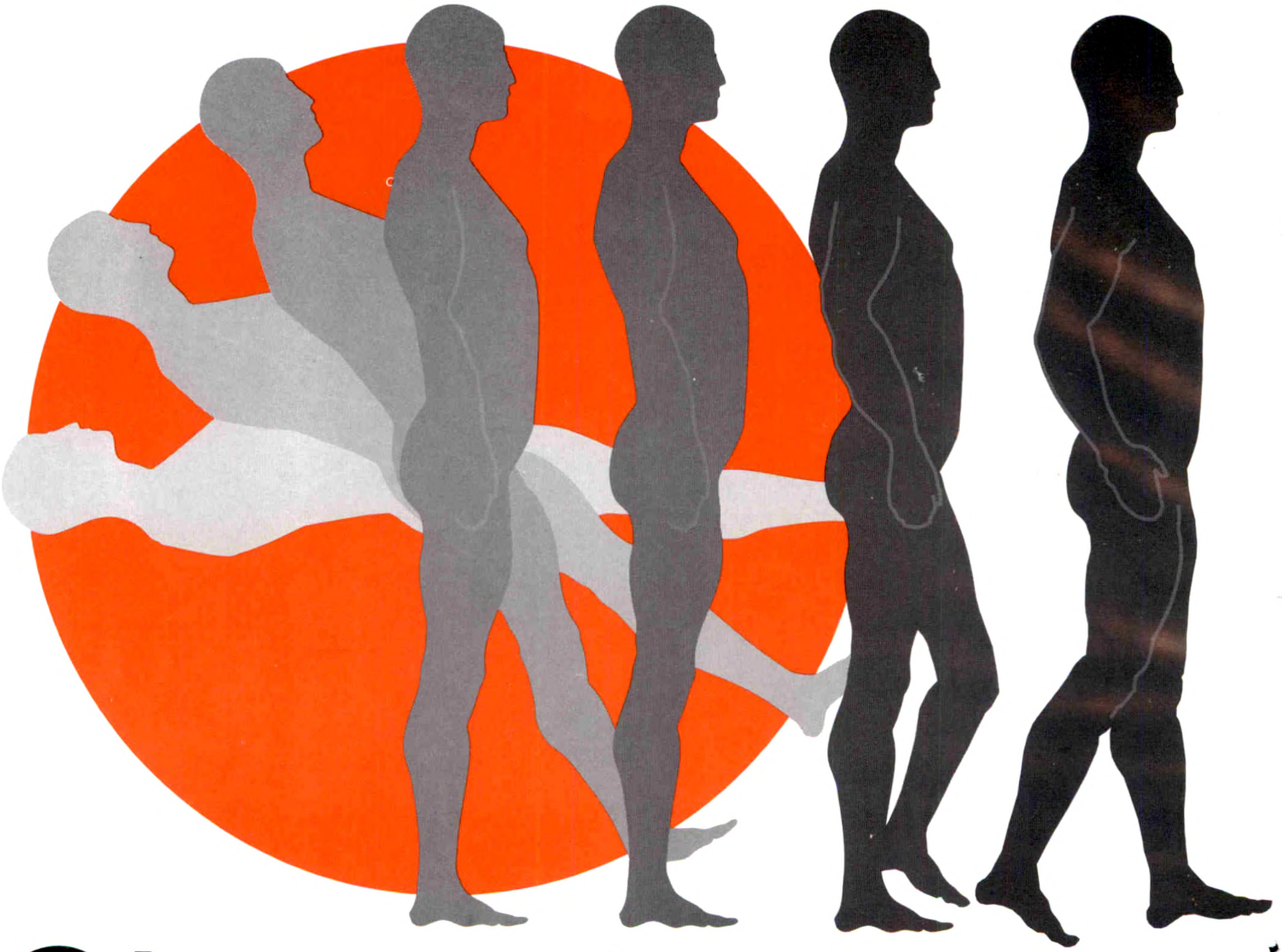

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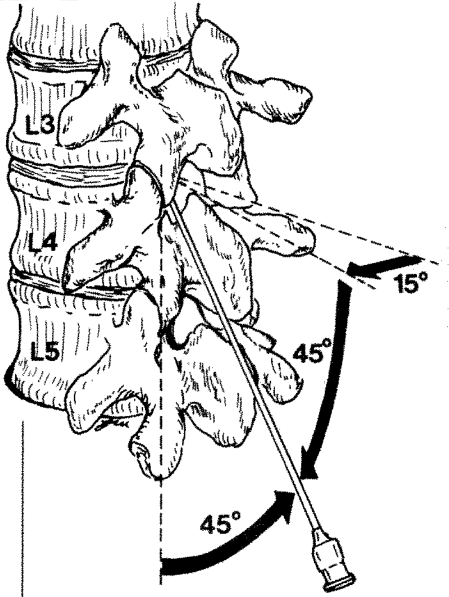

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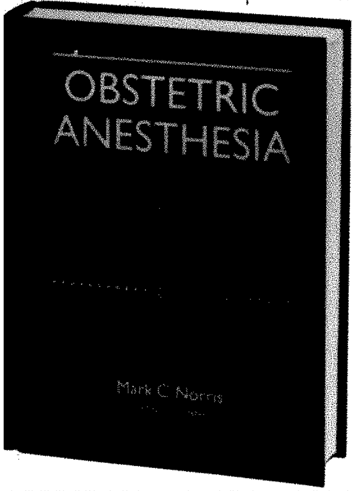

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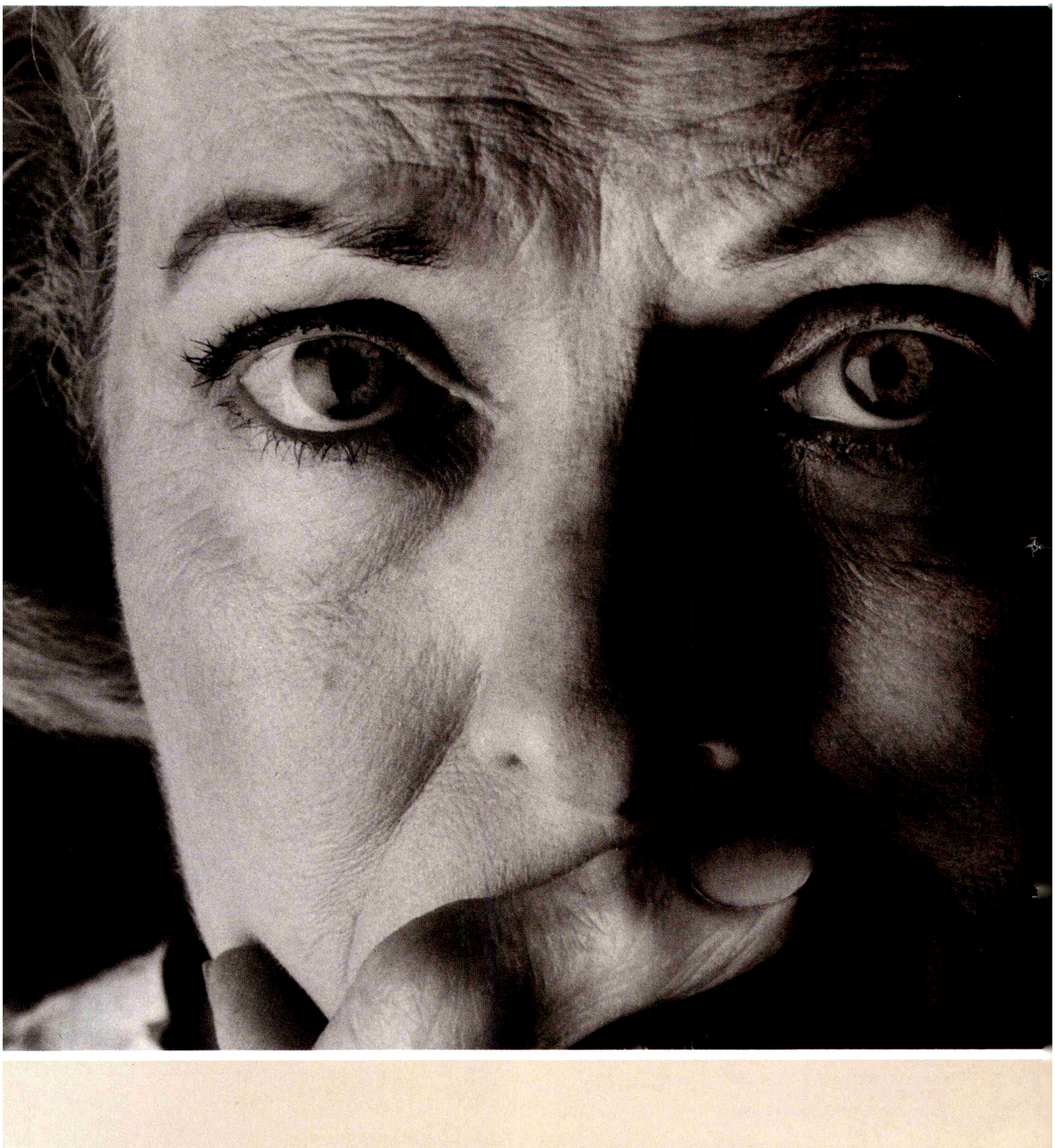

In plasma volume expansion

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HESPAN® is derived from a waxy starch consisting almost entirely of amylopectin.[1] Consequently, there is no risk of serum-transmitted diseases, such as HIV or hepatitis, with HESPAN®.[2] Furthermore, HESPAN® is as effective as albumin for plasma volume expansion.[2,3]

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References: 1. Hespan® prescribing Information. **2.** Waters LM, Christensen MA, Sato RM. Hetastarch: An alternative colloid in burn shock management. *J Burn Care Rehabil.* 1989;10:11-16. **3.** Rackow EC, Falk JL, Fein IA, et al. Fluid resuscitation in circulatory shock: A comparison of the cardiorespiratory effects of albumin, hetastarch, and saline solutions in patients with hypovolemic and septic shock. *Crit Care Med.* 1983;11:839-850.

Hespan®

(6% Hetastarch in 0.9% Sodium Chloride Injection)
BRIEF SUMMARY

CONTRAINDICATIONS

HESPAN is contraindicated in patients with known hypersensitivity to hydroxyethyl starch, or with bleeding disorders, or with congestive heart failure where volume overload is a potential problem. HESPAN should not be used in renal disease with oliguria or anuria not related to hypovolemia.

WARNINGS

Usage in Plasma Volume Expansion: Large volumes may alter the coagulation mechanism. Thus, administration of HESPAN may result in transient prolongation of prothrombin, partial thromboplastin and clotting times. With administration of large doses, the physician should also be alert to the possibility of transient prolongation of bleeding time.

Hematocrit may be decreased and plasma proteins diluted excessively by administration of large volumes of HESPAN. Administration of packed red cells, platelets, and fresh frozen plasma should be considered if excessive dilution occurs.

Use over extended periods: HESPAN has not been adequately evaluated to establish its safety in situations other than leukapheresis that require frequent use of colloidal solutions over extended periods. Certain conditions may affect the safe use of HESPAN on a chronic basis. For example, in patients with subarachnoid hemorrhage where HESPAN is used repeatedly over a period of days for the prevention of cerebral vasospasm, significant clinical bleeding may occur.

Usage in Leukapheresis: Slight declines in platelet counts and hemoglobin levels have been observed in donors undergoing repeated leukapheresis procedures using HESPAN due to the volume expanding effects of HESPAN and to the collection of platelets and erythrocytes. Hemoglobin levels usually return to normal within 24 hours. Hemodilution by HESPAN and saline may also result in 24 hour declines of total protein, albumin, calcium and fibrinogen values. None of these decreases are to a degree recognized to be clinically significant risks to healthy donors.

PRECAUTIONS

General: Regular and frequent clinical evaluation and complete blood counts (CBC) are necessary for proper monitoring of HESPAN® (6% hetastarch in 0.9% sodium chloride injection) use during leukapheresis. If the frequency of leukapheresis is to exceed the guidelines for whole blood donation, you may wish to consider the following additional studies: total leukocyte and platelet counts, leukocyte differential count, hemoglobin and hematocrit, prothrombin time (PT), and partial thromboplastin time (PTT) tests.

The possibility of circulatory overload should be kept in mind. Caution should be used when the risk of pulmonary edema and/or congestive heart failure is increased. Special care should be exercised in patients who have impaired renal clearance since this is the principal way in which hetastarch is eliminated.

Indirect bilirubin levels of 8.3 mg/L (normal 0.0 –7.0 mg/L) have been reported in 2 out of 20 normal subjects who received multiple HESPAN infusions. Total bilirubin was within normal limits at all times; indirect bilirubin returned to normal by 96 hours following the final infusion. The significance, if any, of these elevations is not known; however, caution should be observed before administering HESPAN to patients with a history of liver disease.

HESPAN has been reported to produce hypersensitivity reactions such as wheezing and urticaria. However, hetastarch has not been observed to stimulate antibody formation. If hypersensitivity effects occur, they are readily controlled by discontinuation of the drug and, if necessary, administration of an antihistaminic agent.

Elevated serum amylase levels may be observed temporarily following administration of HESPAN, although no association with pancreatitis has been demonstrated.

If administration is by pressure infusion, all air should be withdrawn or expelled from the bag through the medication port prior to infusion.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies of animals have not been performed to evaluate the carcinogenic potential of hetastarch.

Teratogenic Effects: Pregnancy Category C. Animal reproduction studies have not been conducted with HESPAN. It is also not known whether HESPAN can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. HESPAN should be given to a pregnant woman only if clearly needed.

Nursing Mothers: It is not known whether hetastarch is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when HESPAN is administered to a nursing woman.

Pediatrics: The safety and effectiveness of HESPAN in children have not been established.

ADVERSE REACTIONS

The following have been reported: vomiting, fever, chills, pruritus, submaxillary and parotid glandular enlargement, mild influenza-like symptoms, headaches, muscle pains, peripheral edema of the lower extremities, anaphylactoid reactions (periorbital edema, urticaria, wheezing), bleeding due to hemodilution (see *Warnings*), and circulatory overload and pulmonary edema (see *Precautions*).

DOSAGE AND ADMINISTRATION

Dosage for Acute Use in Plasma Volume Expansion: HESPAN® (6% hetastarch in 0.9% sodium chloride injection) is administered by intravenous infusion only. Total dosage and rate of infusion depend upon the amount of blood or plasma lost and the resultant hemoconcentration. In adults, the amount usually administered is 500 to 1000 mL. Doses of more than 1500 mL per day for the typical 70 kg patient (approximately 20 mL per kg of body weight) are usually not required, although higher doses have been reported in postoperative and trauma patients where severe blood loss has occurred.

Dosage in Leukapheresis: 250 to 700 mL of HESPAN to which citrate anticoagulant has been added is typically administered by aseptic addition to the input line of the centrifugation apparatus at a ratio of 1:8 to 1:13 to venous whole blood. The HESPAN and citrate should be thoroughly mixed to assure effective anticoagulation of blood as it flows through the leukapheresis machine.

Do not use plastic container in series connection.

If administration is controlled by a pumping device, care must be taken to discontinue pumping action before the container runs dry or air embolism may result.

This solution is intended for intravenous administration using sterile equipment. It is recommended that intravenous administration apparatus be replaced at least once every 24 hours.

Use only if solution is clear and container and seals are intact.

The safety and compatibility of other additives have not been established.

Parenteral drug products should be inspected for particulate matter and discoloration prior to administration whenever solution and container permit.

If administration is by pressure infusion, all air should be withdrawn or expelled from the bag through the medication port prior to infusion.

HOW SUPPLIED

HESPAN® (6% hetastarch in 0.9% sodium chloride injection) is supplied sterile and nonpyrogenic in 500 mL EXCEL® Containers packaged 12 per case (NDC 0056-0037-46).

Exposure of pharmaceutical products to heat should be minimized. Avoid excessive heat. Protect from freezing. It is recommended that the product be stored at room temperature (25°C); however, brief exposure up to 40°C does not adversely affect the product.

CAUTION

Federal (USA) law prohibits dispensing without prescription.

To Open

Tear overwrap down at notch and remove solution container. Check for minute leaks by squeezing solution container firmly. If leaks are found, discard solution as sterility may be impaired.

Invert container and carefully inspect the solution in good light for cloudiness, haze, or particulate matter. Any container which is suspect should not be used.

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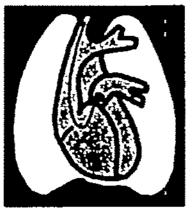

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	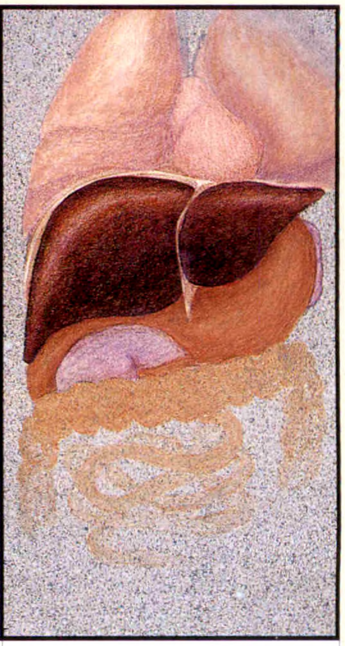
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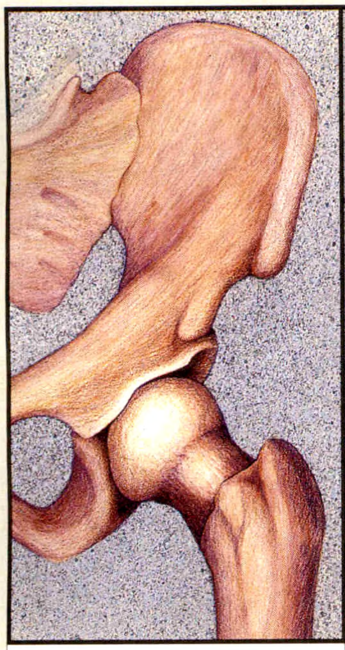
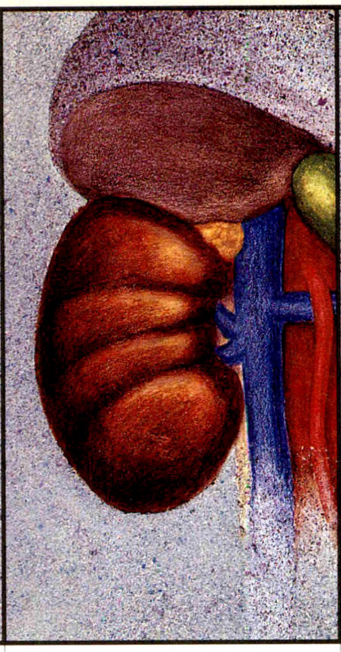
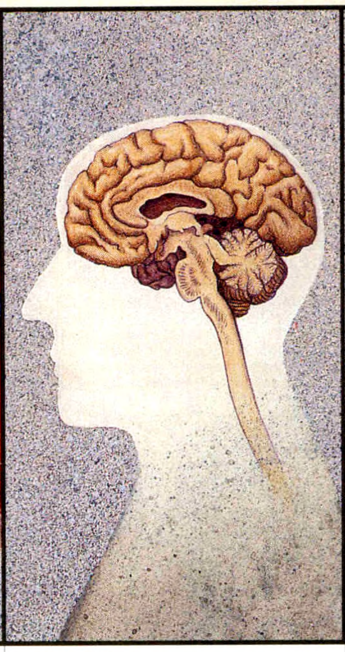
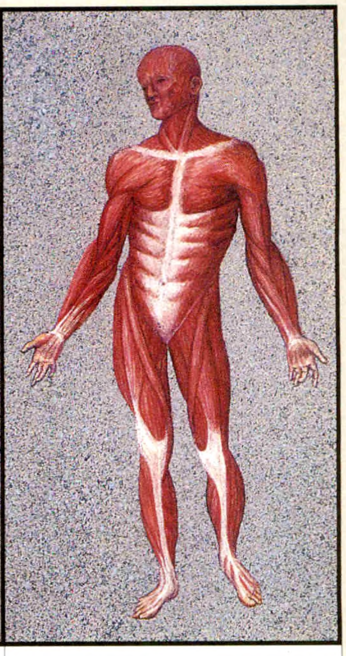
Advantage of Tracrium No difference in recovery from neuromuscular blockade between normal and obese patients.[1]	**Advantage of Tracrium** Clinical response unaffected by hepatic function[2] or patient age.[3]

			
Total hip replacement	**Renal surgery**	**Neurosurgery for trauma**	**Everyday procedures**
Common patient type Elderly women and men	**Common patient type** Both adults and children	**Common patient type** Both adults and children	**Common patient type** Average
Advantage of Tracrium Recovery time unaffected by age.[3]	**Advantage of Tracrium** Recovery time unaffected by renal dysfunction.[2]	**Advantage of Tracrium** Effect unchanged by concomitant anticonvulsant medications (phenytoin, carbamazepine).[4,5]	**Advantage of Tracrium** The same reasons Tracrium is ideal for special patient types make it the choice for everyday procedures.

TRACRIUM® INJECTION

(atracurium besylate) 10 mg/mL

For predictable recovery

TR-Y03368

See brief summary of prescribing information on adjacent page.

TRACRIUM® INJECTION

(atracurium besylate)

Brief Summary
This drug should be used only by adequately trained individuals familiar with its actions, characteristics, and hazards.

INDICATIONS AND USAGE: Tracrium is indicated, as an adjunct to general anesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

CONTRAINDICATIONS: Tracrium is contraindicated in patients known to have a hypersensitivity to it.

WARNINGS: TRACRIUM SHOULD BE USED ONLY BY THOSE SKILLED IN AIRWAY MANAGEMENT AND RESPIRATORY SUPPORT. EQUIPMENT AND PERSONNEL MUST BE IMMEDIATELY AVAILABLE FOR ENDOTRACHEAL INTUBATION AND SUPPORT OF VENTILATION, INCLUDING ADMINISTRATION OF POSITIVE PRESSURE OXYGEN. ADEQUACY OF RESPIRATION MUST BE ASSURED THROUGH ASSISTED OR CONTROLLED VENTILATION. ANTICHOLINESTERASE REVERSAL AGENTS SHOULD BE IMMEDIATELY AVAILABLE. DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION. Tracrium has no known effect on consciousness, pain threshold, or cerebration. It should be used only with adequate anesthesia. Tracrium Injection, which has an acid pH, should not be mixed with alkaline solutions (e.g., barbiturate solutions) in the same syringe or administered simultaneously during intravenous infusion through the same needle. Depending on the resultant pH of such mixtures, Tracrium may be inactivated and a free acid may be precipitated. Tracrium Injection 10 mL multiple dose vials contain benzyl alcohol. Benzyl alcohol has been associated with an increased incidence of neurological and other complications in newborn infants which are sometimes fatal. Tracrium Injection 5 mL ampule and 5 mL single use vials do not contain benzyl alcohol.

PRECAUTIONS: General: Although Tracrium is a less potent histamine releaser than d-tubocurarine or metocurine, the possibility of substantial histamine release in sensitive individuals must be considered. Special caution should be exercised in administering Tracrium to patients in whom substantial histamine release would be especially hazardous (e.g., patients with clinically significant cardiovascular disease) and in patients with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release. In these patients, the recommended initial Tracrium dose is lower (0.3 to 0.4 mg/kg) than for other patients and should be administered slowly or in divided doses over one minute. Since Tracrium has no clinically significant effects on heart rate in the recommended dosage range, it will not counteract the bradycardia produced by many anesthetic agents or vagal stimulation. As a result, bradycardia during anesthesia may be more common with Tracrium than with other muscle relaxants. Tracrium may have profound effects in patients with myasthenia gravis, Eaton-Lambert syndrome, or other neuromuscular diseases in which potentiation of nondepolarizing agents has been noted. The use of a peripheral nerve stimulator is especially important for assessing neuromuscular blockade in these patients. Similar precautions should be taken in patients with severe electrolyte disorders or carcinomatosis. Multiple factors in anesthesia practice are suspected of triggering malignant hyperthermia (MH), a potentially fatal hypermetabolic state of skeletal muscle. Halogenated anesthetic agents and succinylcholine are recognized as the principal pharmacologic triggering agents in MH-susceptible patients; however, since MH can develop in the absence of established triggering agents, the clinician should be prepared to recognize and treat MH in any patient scheduled for general anesthesia. Reports of MH have been rare in cases in which Tracrium has been used. In studies of MH-susceptible animals (swine) and in a clinical study of MH-susceptible patients, Tracrium did not trigger this syndrome. Resistance to nondepolarizing neuromuscular blocking agents may develop in burn patients. Increased doses of nondepolarizing muscle relaxants may be required in burn patients and are dependent on the time elapsed since the burn injury and the size of the burn. The safety of Tracrium has not been established in patients with bronchial asthma. **Long-Term Use in Intensive Care Unit (ICU):** Tracrium has been used to facilitate mechanical ventilation in ICU patients. When there is a need for long-term mechanical ventilation, the benefits to risk ratio of neuromuscular blockade must be considered. There is only limited information on the efficacy and safety of Tracrium administered by long-term (days to weeks) intravenous infusion to facilitate mechanical ventilation in intensive care facilities. For Tracrium, as with other neuromuscular blocking agents used in intensive care facilities, available evidence suggests that there is wide interpatient variability in dosage requirements and that these requirements may change with time. Limited data suggest that Tracrium infusion requirements may increase with prolonged administration in the ICU. As with other neuromuscular blocking agents, little information is available on the plasma levels or clinical consequences of atracurium metabolites following long-term (days to weeks) infusion of Tracrium in the intensive care unit setting. One metabolite of atracurium, laudanosine, when administered alone to laboratory animals, has been associated with cerebral excitatory effects. Physiological effects of laudanosine in humans have not been demonstrated. The effects of hemodialysis, hemoperfusion and hemofiltration on plasma levels of atracurium and its metabolites are unknown. **Drug Interactions:** Drugs which may enhance neuromuscular blocking action of Tracrium include: enflurane; isoflurane; halothane; certain antibiotics, especially the aminoglycosides and polymyxins; lithium; magnesium salts; procainamide; and quinidine. If other muscle relaxants are used during the same procedure, the possibility of a synergistic or antagonist effect should be considered. The prior administration of succinylcholine does not enhance the duration, but quickens the onset and may increase the depth, of neuromuscular blockade induced by Tracrium. Tracrium should not be administered until a patient has recovered from succinylcholine-induced neuromuscular blockade. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** A positive response was observed in the mouse lymphoma assay under conditions which killed over 80% of the treated cells. A far weaker response was observed in the presence of metabolic activation at concentrations which also killed over 80% of the treated cells. **Pregnancy:** ***Teratogenic Effects:*** Pregnancy Category C. Tracrium has been shown to be potentially teratogenic in rabbits, when given in doses up to approximately one-half the human dose. There are no adequate and well-controlled studies in pregnant women. Tracrium should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Labor and Delivery:** It is not known whether muscle relaxants administered during vaginal delivery have immediate or delayed adverse effects on the fetus or increase the likelihood that resuscitation of the newborn will be necessary. The possibility that forceps delivery will be necessary may increase. Tracrium (0.3 mg/kg) has been administered to 26 pregnant women during delivery by cesarean section. No harmful effects were attributable to Tracrium in any of the newborn infants, although small amounts of Tracrium were shown to cross the placental barrier. The possibility of respiratory depression in the newborn infant should always be considered following cesarean section during which a neuromuscular blocking agent has been administered. In patients receiving magnesium sulfate, the reversal of neuromuscular blockade may be unsatisfactory and Tracrium dose should be lowered as indicated. **Nursing Mothers:** It is not known whether this drug is excreted in human milk. Caution should be exercised when Tracrium is administered to a nursing woman. **Pediatric Use:** Safety and effectiveness in children below the age of 1 month have not been established.

ADVERSE REACTIONS: Observed in Controlled Clinical Studies: Tracrium produced few adverse reactions during extensive clinical trials. Most were suggestive of histamine release (see Precautions Section). The overall incidence rate for clinically important adverse reactions was 7/875 or 0.8%. Most adverse reactions were of little clinical significance unless they were associated with significant hemodynamic changes. Substantial vital sign changes greater than or equal to 30% observed in 530 patients, without cardiovascular disease, were as follows: in those patients given the recommended initial dosage range of 0.31 to 0.50 mg/kg of Tracrium, mean arterial pressure increased in 2.8% and decreased in 2.1% of patients while the heart rate increased in 2.8% of these patients. At doses of ≥ 0.60 mg/kg, 14.3% of the studied patients had a decrease in mean arterial pressure while 4.8% had an increase in heart rate. At doses ≤ 0.30 mg/kg, mean arterial pressure increased in 1.9% and decreased in 1.1% of patients, while heart rate increased in 1.6% and decreased in 0.8% of these patients. **Observed in Clinical Practice:** Based on clinical experience in the U.S. and the United Kingdom of approximately 3 million patients given Tracrium the following adverse reactions are among the most frequently reported: *General:* allergic reactions (anaphylactic or anaphylactoid) which, in rare instances, were severe (e.g., cardiac arrest); *Musculoskeletal:* inadequate, prolonged block; *Cardiovascular:* hypotension, vasodilatation (flushing), tachycardia, bradycardia; *Respiratory:* dyspnea, bronchospasm, laryngospasm; *Integumentary:* rash, urticaria, injection site reaction.

STORAGE: Tracrium Injection should be refrigerated at 2° to 8° C (36° to 46° F) to preserve potency. DO NOT FREEZE. Upon removal from refrigeration to room temperature storage conditions (25° C/77° F), use Tracrium Injection within 14 days even if rerefrigerated.

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1. Weinstein JA, Matteo RS, Ornstein E, Schwartz A, Goldstoff M, Thal G. Pharmacodynamics of vecuronium and atracurium in the obese surgical patient. *Anesth Analg.* 1988;67:1149-1153. 2. Ward S, Neill EAM. Pharmacokinetics of atracurium in patients in acute hepatic failure (with acute renal failure). *Br J Anaesth.* 1983;55:1169-1172. 3. d'Hollander A, Luyckx C, Barvais L, DeVille A. Clinical evaluation of atracurium besylate requirement for a stable muscle relaxation during surgery: lack of age-related effects. *Anesthesiology.* 1983;59:237-240. 4. Ornstein E, Matteo RS, Silverberg PA, Schwartz AE, Young WL, Diaz J. Chronic phenytoin therapy and nondepolarizing muscular blockade. *Anesthesiology.* 1985;63:A331. Abstract. 5. Ebrahim Z, Bulkey R, Roth S. Carbamazepine therapy and neuromuscular blockade with atracurium and vecuronium. *Anesth Analg.* 1988;67:S55. Abstract.

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WHY REVERSE BENZODIAZEPINE SEDATION?

A specific antagonist for a prompt return to consciousness

MAZICON® (flumazenil/Roche) is a specific benzodiazepine antagonist, which is indicated to reverse the sedative effects of benzodiazepines following general anesthesia, conscious sedation or in cases of benzodiazepine overdose.

In the clinical practice of anesthesia, there are excellent reasons to reverse benzodiazepine sedation with MAZICON. Intravenous administration of 0.2 mg/min (up to a total of 1 mg) of MAZICON:

- Provides a prompt, controlled awakening from benzodiazepine sedation
- Enhances your control over the depth and duration of sedation
- Facilitates postanesthesia patient assessment
- Returns patients to consciousness sooner—which is reassuring to the patient and the family
- Reverses benzodiazepine sedation only—not narcotics or other CNS agents

When to reverse

There are specific cases where MAZICON reversal of benzodiazepine sedation may be particularly appropriate:

- When postprocedural sedation is not desirable, especially after short surgical or diagnostic procedures
- In elderly patients, who may be at greater risk of adverse effects
- In patients with underlying cardiovascular disease, to minimize the risk of adverse events
- After ambulatory procedures, such as biopsy, dilatation and curettage, hernia repair, arthroscopic surgery, plastic surgery or ophthalmic surgery—in these situations, reversal of sedation with MAZICON allows the patient to cooperate, so that patient management can be facilitated

Adverse effects

The most common side effects in clinical trials were nausea and vomiting (11%), dizziness (10%), agitation (3% to 9%) and injection-site pain (3% to 9%).

MAZICON has been associated with seizures, most often in patients on benzodiazepines for long-term sedation or patients showing signs of serious cyclic antidepressant overdose. Practitioners should individualize the dosage and be prepared to manage seizures.

Important safety information

Patients should be monitored for possible resedation, respiratory depression or other residual effects of benzodiazepines.

The availability of MAZICON does not diminish the need for prompt detection of hypoventilation and the need to be prepared to effectively intervene by establishing an airway and assisting ventilation. MAZICON has not been established as an effective treatment for benzodiazepine-induced hypoventilation.

Contraindicated in hypersensitivity to benzodiazepines or MAZICON; in patients taking benzodiazepines for control of potentially life-threatening conditions; and in patients showing signs of serious cyclic antidepressant overdose. In patients who are dependent on benzodiazepines, MAZICON may precipitate withdrawal syndromes.

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IDEAS IN ANESTHESIA

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AN ONGOING SERIES

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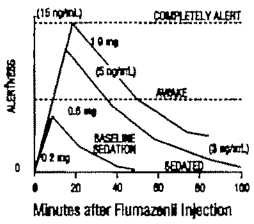
Please see following pages for complete product information.

MAZICON™
(flumazenil/Roche)
INJECTION

DESCRIPTION: MAZICON™ (flumazenil/Roche) is a benzodiazepine receptor antagonist. Chemically, flumazenil is ethyl 8-fluoro-5,6-dihydro-5-methyl-6-oxo-4H-imidazo[1,5-a](1,4) benzodiazepine-3-carboxylate. Flumazenil has an imidazobenzodiazepine structure, a calculated molecular weight of 303.3.
Flumazenil is a white to off-white crystalline compound with an octanol:buffer partition coefficient of 14 to 1 at pH 7.4. It is insoluble in water but slightly soluble in acidic aqueous solutions. MAZICON is available as a sterile parenteral dosage form for intravenous administration. Each mL contains 0.1 mg of flumazenil compounded with 1.8 mg of methylparaben, 0.2 mg of propylparaben, 0.9% sodium chloride, 0.01% edetate disodium, and 0.01% acetic acid; the pH is adjusted to approximately 4 with hydrochloric acid and/or, if necessary, sodium hydroxide.

CLINICAL PHARMACOLOGY: Flumazenil, an imidazobenzodiazepine derivative, antagonizes the actions of benzodiazepines on the central nervous system. Flumazenil competitively inhibits the activity at the benzodiazepine recognition site on the GABA/benzodiazepine receptor complex. Flumazenil is a weak partial agonist in some animal models of activity, but has little or no agonist activity in man.
Flumazenil does not antagonize the central nervous system effects of drugs affecting GABA-ergic neurons by means other than the benzodiazepine receptor (including ethanol, barbiturates, or general anesthetics) and does not reverse the effects of opioids.
PHARMACODYNAMICS: Intravenous MAZICON has been shown to antagonize sedation, impairment of recall and psychomotor impairment produced by benzodiazepines in healthy human volunteers.
The duration and degree of reversal of benzodiazepine effects are related to the dose and plasma concentrations of flumazenil as shown in the following data from a study in normal volunteers.

Magnitude and Duration of Reversal of Sedation as a Function of Flumazenil Dose*
Flumazenil doses of 0.2, 0.6 & 1.0 mg
(blood level in ng/mL)



*Sedation produced by midazolam infusion at a rate of 0.06 - 0.20 mg/kg/hr in healthy volunteers

Generally, doses of approximately 0.1 to 0.2 mg (corresponding to peak plasma levels of 3 to 6 ng/mL) produce partial antagonism, whereas higher doses of 0.4 to 1.0 mg (peak plasma levels of 12 to 28 ng/mL) usually produce complete antagonism in patients who have received the usual sedating doses of benzodiazepines. The onset of reversal is usually evident within 1 to 2 minutes after the injection is completed. Eighty percent response will be reached within 3 minutes, with the peak effect occurring at 6 to 10 minutes. The duration and degree of reversal are related to the plasma concentration of the sedating benzodiazepine as well as the dose of MAZICON given.
In healthy volunteers, MAZICON did not alter intraocular pressure when given alone and reversed the decrease in intraocular pressure seen after administration of midazolam.
PHARMACOKINETICS: After IV administration, plasma concentrations of flumazenil follow a two compartment open pharmacokinetic model with an initial distribution half-life of 7 to 15 minutes and a terminal half-life of 41 to 79 minutes. Peak concentrations of flumazenil are proportional to dose, with an apparent initial volume of distribution of 0.5 L/kg. After redistribution the apparent volume of distribution (V_{ss}) ranges from 0.77 to 1.60 L/kg. Protein binding is approximately 50% and the drug shows no preferential partitioning into red blood cells. Flumazenil is a highly extracted drug. Clearance of flumazenil occurs primarily by hepatic metabolism and is dependent on hepatic blood flow. In pharmacokinetic studies of normal volunteers, total clearance ranges from 0.7 to 1.3 L/hr/kg, with less than 1% of the administered dose eliminated unchanged in the urine. The major metabolites of flumazenil identified in urine are the de-ethylated free acid and its glucuronide conjugate. In preclinical studies there was no evidence of pharmacologic activity exhibited by the de-ethylated free acid. Elimination of radiolabelled drug is essentially complete within 72 hours, with 90% to 95% of the radioactivity appearing in urine and 5% to 10% in the feces.

Pharmacokinetic Parameters Following a 5-minute Infusion of a total of 1.0 mg of MAZICON Mean (Coefficient of variation, Range)

C_{max} (ng/mL)	24 (38%, 11-43)
AUC (ng•hr/mL)	15 (22%, 10-22)
V_{ss} (L/kg)	1 (24%, 0.8-1.6)
Cl (L/hr/kg)	1 (20%, 0.7-1.4)
Half-life (min)	54 (21%, 41-79)

The pharmacokinetics of flumazenil are not significantly affected by gender, age, renal failure (creatinine clearance <10 mL/min), or hemodialysis beginning 1 hour after drug administration. Mean total clearance is decreased to 40% to 60% of normal in patients with moderate liver dysfunction and to 25% of normal in patients with severe liver dysfunction compared with age-matched healthy subjects. This results in a prolongation of the half-life from 0.8 hours in healthy subjects to 1.3 hours in patients with moderate hepatic impairment and 2.4 hours in severely impaired patients. Ingestion of food during an intravenous infusion of the drug results in a 50% increase in clearance, most likely due to the increased hepatic blood flow that accompanies a meal. The pharmacokinetic profile of flumazenil is unaltered in the presence of benzodiazepine agonists and the kinetic profiles of those benzodiazepines are unaltered by flumazenil.

CLINICAL TRIALS: MAZICON has been administered to reverse the effects of benzodiazepines in conscious sedation, general anesthesia, and the management of suspected benzodiazepine overdose.
CONSCIOUS SEDATION: MAZICON was studied in four trials in 970 patients who received an average of 30 mg diazepam or 10 mg midazolam for sedation (with or without a narcotic) in conjunction with both inpatient and outpatient diagnostic or surgical procedures. MAZICON was effective in reversing the sedating and psychomotor effects of the benzodiazepine, however, amnesia was less completely and less consistently reversed. In these studies, MAZICON was administered as an initial dose of 0.4 mg I.V. (two doses of 0.2 mg) with additional 0.2 mg doses as needed to achieve complete awakening, up to a maximum total dose of 1.0 mg. Seventy-eight percent of patients receiving flumazenil responded by becoming completely alert. Of those patients, approximately half responded to doses of 0.4 to 0.6 mg, while the other half responded to doses of 0.8 to 1.0 mg. Adverse effects were infrequent in patients who received 1 mg of MAZICON or less, although injection site pain, agitation and anxiety did occur. Reversal of sedation was not associated with any increase in the frequency of inadequate analgesia or increase in narcotic demand in these studies. While most patients remained alert throughout the 3 hour post-procedure observation period, resedation was observed to occur in 3% to 9% of the patients, and was most common in patients who had received high doses of benzodiazepine. (See PRECAUTIONS.)
GENERAL ANESTHESIA: MAZICON was studied in four trials in 644 patients who received midazolam as an induction and/or maintenance agent in both balanced and inhalational anesthesia. Midazolam was generally administered in doses ranging from 5 to 80 mg, alone and/or in conjunction with muscle relaxants, nitrous oxide, regional or local anesthetics, narcotics and/or inhalational anesthetics. Flumazenil was given as an initial dose of 0.2 mg IV, with additional 0.2 mg doses as needed to reach a complete response, up to a maximum total dose of 1.0 mg. These doses were effective in reversing sedation and restoring psychomotor function, but did not completely restore memory as tested by picture recall. MAZICON was not as effective in the reversal of sedation in patients who had received multiple anesthetic agents in addition to benzodiazepines.
Eighty-one percent of patients sedated with midazolam responded to flumazenil by becoming completely alert or just slightly drowsy. Of those patients, 36% responded to doses of 0.4 to 0.6 mg, while 64% responded to doses of 0.8 to 1.0 mg.
Resedation in patients who responded to MAZICON occurred in 10% to 15% of patients studied and was more common with larger doses of midazolam (>20 mg), long procedures (>60 minutes) and use of neuromuscular blocking agents. (See PRECAUTIONS.)
MANAGEMENT OF SUSPECTED BENZODIAZEPINE OVERDOSE: MAZICON was studied in two trials in 497 patients who were presumed to have taken an overdose of a benzodiazepine, either alone or in combination with a variety of other agents. In these trials, 299 patients were proven to have taken a benzodiazepine as part of the overdose, and 80% of the 148 who received MAZICON responded by an improvement in level of consciousness. Of the patients who responded to flumazenil, 75% responded to a total dose of 1.0 to 3.0 mg. Reversal of sedation was associated with an increased frequency of symptoms of CNS excitation. Of the

patients treated with flumazenil, 1% to 3% were treated for agitation or anxiety. Serious side effects were uncommon, but six seizures were observed in 446 patients treated with flumazenil in these studies. Four of these 6 patients had ingested a large dose of cyclic antidepressants, which increased the risk of seizures. (See WARNINGS.)

INDIVIDUALIZATION OF DOSAGE: GENERAL PRINCIPLES: The serious adverse effects of MAZICON are related to the reversal of benzodiazepine effects. Using more than the minimally effective dose of MAZICON is tolerated by most patients but may complicate the management of patients who are physically dependent on benzodiazepines or patients who are depending on benzodiazepines for therapeutic effect (such as suppression of seizures in cyclic antidepressant overdose).
In high-risk patients, it is important to administer the smallest amount of MAZICON that is effective. The 1-minute wait between individual doses in the dose-titration recommended for general clinical populations may be too short for high risk patients. This is because it takes 6 to 10 minutes for any single dose of flumazenil to reach full effects. Practitioners should slow the rate of administration of MAZICON administered to high risk patients as recommended below.
ANESTHESIA AND CONSCIOUS SEDATION: MAZICON is well tolerated at the recommended doses in individuals who have no tolerance to (or dependence on) benzodiazepines. The recommended dosages and titration rates in anesthesia and conscious sedation (0.2 to 1.0 mg given at 0.2 mg/min) are well tolerated in patients receiving the drug for reversal of a single benzodiazepine exposure in most clinical settings (see Adverse Events). The major risk will be resedation because the duration of effect of a long-acting (or large dose of a short-acting) benzodiazepine may exceed that of MAZICON. Resedation may be treated by giving a repeat dose at no less than 20-minute intervals. For repeat treatment, no more than 1.0 mg (at 0.2 mg/min doses) should be given at any one time and no more than 3.0 mg should be given in any one hour.
OVERDOSE PATIENTS: The risk of confusion, agitation, emotional lability and perceptual distortion with the doses recommended in patients with benzodiazepine overdose (3 to 5 mg administered as 0.5 mg/min) may be greater than that expected with lower doses and slower administration. The recommended doses represent a compromise between a desirable slow awakening and the need for prompt response and a persistent effect in the overdose situation. If circumstances permit, the physician may elect to use the 0.2 mg/minute titration rate to slowly awaken the patient over 5 to 10 minutes, which may help to reduce signs and symptoms on emergence.
MAZICON has no effect in cases where benzodiazepines are not responsible for sedation. Once doses of 3 to 5 mg have been reached without clinical response, additional MAZICON is likely to have no effect.
PATIENTS TOLERANT TO BENZODIAZEPINES: MAZICON may cause benzodiazepine withdrawal symptoms in individuals who have been taking benzodiazepines long enough to have some degree of tolerance. Patients who had been taking benzodiazepines prior to entry into the MAZICON trials who were given flumazenil in doses over 1 mg experienced withdrawal-like events 2 to 5 times more frequently than patients who received less than 1 mg.
In patients who may have tolerance to benzodiazepines, as indicated by clinical history or by the need for larger than usual doses of benzodiazepine, slower titration rates of 0.1 mg/min and lower total doses may help reduce the frequency of emergent confusion and agitation. In such cases special care must be taken to monitor the patients for resedation because of the lower doses of MAZICON used.
PATIENTS PHYSICALLY DEPENDENT ON BENZODIAZEPINES: MAZICON is known to precipitate withdrawal seizures in patients who are physically dependent on benzodiazepines, even if such dependence was established in a relatively few days of high dose sedation in Intensive Care Unit environments. The risk of either seizures or resedation in such cases is high and patients have experienced seizures before regaining consciousness. MAZICON should be used in such settings with extreme caution, since the use of flumazenil in this situation has not been studied and no information as to dose and rate of titration is available. MAZICON should be used in such patients only if the potential benefits of using the drug outweigh the risks of precipitated seizures. Physicians are directed to the scientific literature for the most current information in this area.

INDICATIONS AND USAGE: MAZICON is indicated for the complete or partial reversal of the sedative effects of benzodiazepines in cases where general anesthesia has been induced and/or maintained with benzodiazepines, where sedation has been produced with benzodiazepines for diagnostic and therapeutic procedures, and for the management of benzodiazepine overdose.

CONTRAINDICATIONS: MAZICON is contraindicated:
- in patients with a known hypersensitivity to flumazenil or to benzodiazepines.
- in patients who have been given a benzodiazepine for control of a potentially life-threatening condition (*e.g.* control of intracranial pressure or status epilepticus).
- in patients who are showing signs of serious cyclic antidepressant overdose. (See WARNINGS.)

WARNINGS:

**THE USE OF MAZICON HAS BEEN ASSOCIATED WITH THE OCCURRENCE OF SEIZURES.
THESE ARE MOST FREQUENT IN PATIENTS WHO HAVE BEEN ON BENZODIAZEPINES FOR LONG-TERM SEDATION OR IN OVERDOSE CASES WHERE PATIENTS ARE SHOWING SIGNS OF SERIOUS CYCLIC ANTIDEPRESSANT OVERDOSE.
PRACTITIONERS SHOULD INDIVIDUALIZE THE DOSAGE OF MAZICON AND BE PREPARED TO MANAGE SEIZURES.**

**Risk of Seizures: The reversal of benzodiazepine effects may be associated with the onset of seizures in certain high-risk populations. Possible risk factors for seizures include: concurrent major sedative-hypnotic drug withdrawal, recent therapy with repeated doses of parenteral benzodiazepines, myoclonic jerking or seizure activity prior to flumazenil administration in overdose cases, or concurrent cyclic antidepressant poisoning.
MAZICON is not recommended in cases of serious cyclic antidepressant poisoning, as manifested by motor abnormalities (twitching, rigidity, focal seizure), dysrhythmia (wide QRS, ventricular dysrhythmia, heart block), anticholinergic signs (mydriasis, dry mucosa, hypo-peristalsis), and cardiovascular collapse at presentation. In such cases MAZICON should be withheld and the patient should be allowed to remain sedated (with ventilatory and circulatory support as needed) until the signs of antidepressant toxicity have subsided. Treatment with MAZICON has no known benefit to the seriously ill mixed-overdose patient other than reversing sedation and should not be used in cases where seizures (from any cause) are likely.
Most convulsions associated with flumazenil administration require treatment and have been successfully managed with benzodiazepines, phenytoin or barbiturates. Because of the presence of flumazenil, higher than usual doses of benzodiazepines may be required.**

**HYPOVENTILATION: Patients who have received MAZICON for the reversal of benzodiazepine effects (after conscious sedation or general anesthesia) should be monitored for resedation, respiratory depression, or other residual benzodiazepine effects for an appropriate period (up to 120 minutes) based on the dose and duration of effect of the benzodiazepine employed.
This is because MAZICON has not been established as an effective treatment for hypoventilation due to benzodiazepine administration. The availability of flumazenil does not diminish the need for prompt detection of hypoventilation and the ability to effectively intervene by establishing an airway and assisting ventilation.
MAZICON may not fully reverse postoperative airway problems or ventilatory insufficiency induced by benzodiazepines. In addition, even if MAZICON is initially effective, such problems may recur because the effects of MAZICON wear off before the effects of many benzodiazepines.
Overdose cases should always be monitored for resedation until the patients are stable and resedation is unlikely.**

PRECAUTIONS: RETURN OF SEDATION: MAZICON may be expected to improve the alertness of patients recovering from a procedure involving sedation or anesthesia with benzodiazepines, but should not be substituted for an adequate period of post-procedure monitoring. The availability of MAZICON does not reduce the risks associated with the use of large doses of benzodiazepines for sedation.
Patients should be monitored for resedation, respiratory depression (see WARNINGS), or other persistent or recurrent agonist effects for an adequate period of time after administration of MAZICON.
Resedation is least likely in cases where MAZICON is administered to reverse a low dose of a short-acting benzodiazepine (<10 mg midazolam). It is most likely in cases where a large single or cumulative dose of a benzodiazepine has been given in the course of a long procedure along with neuromuscular blocking agents and multiple anesthetic agents.
Profound resedation was observed in 1% to 3% of patients in the clinical studies. In clinical situations where resedation must be prevented, physicians may wish to repeat the initial dose (up to 1 mg of MAZICON given at 0.2 mg/min) at 30 minutes and possibly again at 60 minutes. This dosage schedule, although not studied in clinical trials, was effective in preventing resedation in a pharmacologic study in normal volunteers.
USE IN THE ICU: MAZICON should be used with caution in the Intensive Care Unit because of the increased risk of unrecognized benzodiazepine dependence in such settings. MAZICON may produce convulsions in patients physically dependent on benzodiazepines. (See INDIVIDUALIZATION OF DOSAGE AND WARNINGS.)
Administration of MAZICON to diagnose benzodiazepine-induced sedation in the Intensive Care Unit is not recommended due to the risk of adverse events as described above. In addition, the prognostic significance of a patient's failure to respond to flumazenil in cases confounded by metabolic disorder, traumatic injury, drugs other than benzodiazepines, or any other reasons not associated with benzodiazepine receptor occupancy is not known.

USE IN OVERDOSE: **MAZICON** is intended as an adjunct to, not as a substitute for, proper management of airway, assisted breathing, circulatory access and support, internal decontamination by lavage and charcoal, and adequate clinical evaluation.

Necessary measures should be instituted to secure airway, ventilation and intravenous access prior to administering flumazenil. Upon arousal patients may attempt to withdraw endotracheal tubes and/or intravenous lines as the result of confusion and agitation following awakening.

HEAD INJURY: **MAZICON** should be used with caution in patients with head injury as it may be capable of precipitating convulsions or altering cerebral blood flow in patients receiving benzodiazepines. It should be used only by practitioners prepared to manage such complications should they occur.

USE WITH NEUROMUSCULAR BLOCKING AGENTS: **MAZICON** should not be used until the effects of neuromuscular blockade have been fully reversed.

USE IN PSYCHIATRIC PATIENTS: **MAZICON** has been reported to provoke panic attacks in patients with a history of panic disorder.

PAIN ON INJECTION: To minimize the likelihood of pain or inflammation at the injection site, MAZICON should be administered through a freely flowing intravenous infusion into a large vein. Local irritation may occur following extravasation into perivascular tissues.

USE IN RESPIRATORY DISEASE: The primary treatment of patients with serious lung disease who experience serious respiratory depression due to benzodiazepines should be appropriate ventilatory support (See PRECAUTIONS) rather than the administration of MAZICON. Flumazenil is capable of partially reversing benzodiazepine-induced alterations in ventilatory drive in healthy volunteers, but has not been shown to be clinically effective.

USE IN CARDIOVASCULAR DISEASE: **MAZICON** did not increase the work of the heart when used to reverse benzodiazepines in cardiac patients when given at a rate of 0.1 mg/min in total doses of less than 0.5 mg in studies reported in the clinical literature. Flumazenil alone had no significant effects on cardiovascular parameters when administered to patients with stable ischemic heart disease.

USE IN LIVER DISEASE: The clearance of **MAZICON** is reduced to 40% to 60% of normal in patients with mild to moderate hepatic disease and to 25% of normal in patients with severe hepatic dysfunction. (See PHARMACOKINETICS.) While the dose of flumazenil used for initial reversal of benzodiazepine effects is not affected, repeat doses of the drug in liver disease should be reduced in size or frequency.

USE IN DRUG AND ALCOHOL DEPENDENT PATIENTS: **MAZICON** should be used with caution in patients with alcoholism and other drug dependencies due to the increased frequency of benzodiazepine tolerance and dependence observed in these patient populations.

MAZICON is not recommended either as a treatment for benzodiazepine dependence or for the management of protracted benzodiazepine abstinence syndromes, as such use has not been studied.

The administration of flumazenil can precipitate benzodiazepine withdrawal in animals and man. This has been seen in healthy volunteers treated with therapeutic doses of oral lorazepam for up to 2 weeks who exhibited effects such as hot flushes, agitation and tremor when treated with cumulative doses of up to 3 mg doses of flumazenil.

Similar adverse experiences suggestive of flumazenil precipitation of benzodiazepine withdrawal have occurred in some patients in clinical trials. Such patients had a short-lived syndrome characterized by dizziness, mild confusion, emotional lability, agitation (with signs and symptoms of anxiety), and mild sensory distortions. This response was dose-related, most common at doses above 1 mg, rarely required treatment other than reassurance and was usually short lived. When required (5 to 10 cases), these patients were successfully treated with usual doses of a barbiturate, a benzodiazepine, or other sedative drug.

Practitioners should assume that flumazenil administration may trigger dose-dependent withdrawal syndromes in patients with established physical dependence on benzodiazepines and may complicate the management of withdrawal syndromes for alcohol, barbiturates and cross-tolerant sedatives.

DRUG INTERACTIONS: Interaction with central nervous system depressants other than benzodiazepines has not been specifically studied; however, no deleterious interactions were seen when **MAZICON** was administered after narcotics, inhalational anesthetics, muscle relaxants and muscle relaxant antagonists administered in conjunction with sedation or anesthesia.

Particular caution is necessary when using MAZICON in cases of mixed drug overdosage since the toxic effects (such as convulsions and cardiac dysrhythmias) of other drugs taken in overdose (especially cyclic antidepressants) may emerge with the reversal of the benzodiazepine effect by flumazenil. (See WARNINGS.)

The pharmacokinetics of benzodiazepines are unaltered in the presence of flumazenil.

USE IN AMBULATORY PATIENTS: The effects of MAZICON may wear off before a long-acting benzodiazepine is completely cleared from the body. In general, if a patient shows no signs of sedation within 2 hours after a 1.0 mg dose of flumazenil, serious resedation at a later time is unlikely. An adequate period of observation must be provided for any patient in whom either long-acting benzodiazepines (such as diazepam) or large doses of short-acting benzodiazepines (such as >10 mg of midazolam) have been used. (See INDIVIDUALIZATION OF DOSAGE.)

Because of the increased risk of adverse reactions in patients who have been taking benzodiazepines on a regular basis, it is particularly important that physicians query carefully about benzodiazepine, alcohol and sedative use as part of the history prior to any procedure in which the use of **MAZICON** is planned. (See DRUG AND ALCOHOL DEPENDENT PATIENTS.)

INFORMATION FOR PATIENTS: **MAZICON** does not consistently reverse amnesia. Patients cannot be expected to remember information told to them in the post-procedure period and instructions given to patients should be reinforced in writing or given to a responsible family member. Physicians are advised to discuss with their patients, both before surgery and at discharge, that although the patient may feel alert at the time of discharge, the effects of the benzodiazepine may recur. As a result, the patient should be instructed, preferably in writing, that their memory and judgment may be impaired and specifically advised:

1. Not to engage in any activities requiring complete alertness, and not to operate hazardous machinery or a motor vehicle until at least 18 to 24 hours after discharge, and it is certain no residual sedative effects of the benzodiazepine remain.
2. Not to take any alcohol or non-prescription drugs for 18 to 24 hours after flumazenil administration or if the effects of the benzodiazepine persist.

LABORATORY TESTS: No specific laboratory tests are recommended to follow the patient's response or to identify possible adverse reactions.

DRUG/LABORATORY TEST INTERACTIONS: The possible interaction of flumazenil with commonly used laboratory tests has not been evaluated.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Carcinogenesis: No studies in animals to evaluate the carcinogenic potential of flumazenil have been conducted.

Mutagenesis: No evidence for mutagenicity was noted in the Ames test using five different tester strains. Assays for mutagenic potential in *S. cerevisiae* D7 and in Chinese hamster cells were considered to be negative as were blastogenesis assays *in vitro* in peripheral human lymphocytes and *in vivo* in a mouse micronucleus assay. Flumazenil caused a slight increase in unscheduled DNA synthesis in rat hepatocyte culture at concentrations which were also cytotoxic; no increase in DNA repair was observed in male mouse germ cells in an *in vivo* DNA repair assay.

Impairment of fertility: A reproduction study in male and female rats did not show any impairment of fertility at oral dosages of 125 mg/kg/day. From the available data on the area under the curve (AUC) in animals and man the dose represented 120 x the human exposure from a maximum recommended intravenous dose of 5 mg.

PREGNANCY: CATEGORY C. There are no adequate and well-controlled studies of the use of flumazenil in pregnant women. Flumazenil should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Teratogenic Effects: Flumazenil has been studied for teratogenicity in rats and rabbits following oral treatments of up to 150 mg/kg/day. The treatments during the major organogenesis were on days 6 to 15 of gestation in the rat and days 6 to 18 of gestation in the rabbit. No teratogenic effects were observed in rats or rabbits at 150 mg/kg; the dose, based on the available data on the area under the plasma concentration-time curve (AUC) represented 120 x to 600 x the human exposure from a maximum recommended intravenous dose of 5 mg in humans. In rabbits, embryocidal effects (as evidenced by increased pre-implantation and post-implantation losses) were observed at 50 mg/kg or 200 x the human exposure from a maximum recommended intravenous dose of 5 mg. The no-effect dose of 15 mg/kg in rabbits represents 60 x the human exposure.

Nonteratogenic Effects: An animal reproduction study was conducted in rats at oral dosages of 5, 25 and 125 mg/kg/day of flumazenil. Pup survival was decreased during the lactating period, pup liver weight at weaning was increased for the high-dose group (125 mg/kg/day) and incisor eruption and ear opening in the offspring were delayed; the delay in ear opening was associated with a delay in the appearance of the auditory startle response. No treatment-related adverse effects were noted for the other dose groups. Based on the available data from AUC, the effect level (125 mg/kg), represents 120 x the human exposure from 5 mg, the maximum recommended intravenous dose in humans. The no-effect level represents 24 x the human exposure from an intravenous dose of 5 mg.

LABOR AND DELIVERY: The use of **MAZICON** to reverse the effects of benzodiazepines used during labor and delivery is not recommended because the effects of the drug in the newborn are unknown.

NURSING MOTHERS: Caution should be exercised when deciding to administer **MAZICON** to a nursing woman because it is not known whether flumazenil is excreted in human milk.

PEDIATRIC USE: **MAZICON** is not recommended for use in children (either for the reversal of sedation, the management of overdose or the resuscitation of the newborn), as no clinical studies have been performed to determine the risks, benefits and dosages to be used.

GERIATRIC USE: The pharmacokinetics of flumazenil have been studied in the elderly and are not significantly different from younger patients. Several studies of **MAZICON** in patients over the age of 65 and one study in patients over the age of 80 suggest that while the doses of benzodiazepine used to induce sedation should be reduced, ordinary doses of **MAZICON** may be used for reversal.

ADVERSE REACTIONS: SERIOUS ADVERSE REACTIONS: Deaths have occurred in patients who received MAZICON in a variety of clinical settings. The majority of deaths occurred in patients with serious underlying disease or in patients who had ingested large amounts of non-benzodiazepine drugs, (usually cyclic antidepressants) as part of an overdose.

Serious adverse events have occurred in all clinical settings, and convulsions are the most common serious adverse event reported. **MAZICON** administration has been associated with the onset of convulsions in patients who are relying on benzodiazepine effects to control seizures, are physically dependent on benzodiazepines, or who have ingested large doses of other drugs. (See WARNINGS.)

Two of the 446 patients who received **MAZICON** in controlled clinical trials for the management of a benzodiazepine overdosage had cardiac dysrhythmias (1 ventricular tachycardia, 1 junctional tachycardia).

ADVERSE EVENTS IN CLINICAL STUDIES: The following adverse reactions were considered to be related to **MAZICON** administration (both alone and for the reversal of benzodiazepine effects) and were reported in studies involving 1875 individuals who received flumazenil in controlled trials. Adverse events most frequently associated with flumazenil alone were limited to dizziness, injection site pain, increased sweating, headache and abnormal or blurred vision (3% to 9%).

BODY AS A WHOLE: Fatigue (asthenia, malaise), Headache, Injection Site Pain*, Injection Site Reaction (thrombophlebitis, skin abnormality, rash)

CARDIOVASCULAR SYSTEM: Cutaneous vasodilation (sweating, flushing, hot flushes)

DIGESTIVE SYSTEM: Nausea and Vomiting (11%)

NERVOUS SYSTEM: Agitation (anxiety, nervousness, dry mouth, tremor, palpitations, insomnia, dyspnea, hyperventilation)*, Dizziness (vertigo, ataxia) (10%), Emotional lability (crying abnormal, depersonalization, euphoria, increased tears, depression, dysphoria, paranoia).

SPECIAL SENSES: Abnormal Vision (visual field defect, diplopia), Paresthesia (sensation abnormal, hypoesthesia)

All adverse reactions occurred in 1% to 3% of cases unless otherwise marked.

*Indicates reaction in 3% to 9% of cases.

Observed percentage reported if greater than 9%.

The following adverse events were observed infrequently (less than 1%) in the clinical studies, but were judged as probably related to **MAZICON** administration and/or reversal of benzodiazepine effects:

NERVOUS SYSTEM: Confusion (difficulty concentrating, delirium), Convulsions (see WARNINGS), Somnolence (stupor).

SPECIAL SENSES: Abnormal Hearing (transient hearing impairment, hyperacusis, tinnitus).

The following adverse events occurred with frequencies less than 1% in the clinical trials. Their relationship to **MAZICON** administration is unknown, but they are included as alerting information for the physician.

BODY AS A WHOLE: Rigors, shivering.

CARDIOVASCULAR: Arrhythmia (atrial, nodal, ventricular extrasystoles), bradycardia, tachycardia, hypertension, chest pain.

DIGESTIVE SYSTEM: Hiccup.

NERVOUS SYSTEM: Speech disorder (dysphonia, thick tongue).

Not included in this list is operative site pain that occurred with the same frequency in patients receiving placebo as in patients receiving flumazenil for reversal of sedation following a surgical procedure.

DRUG ABUSE AND DEPENDENCE: MAZICON acts as a benzodiazepine antagonist, blocks the effects of benzodiazepines in animals and man, antagonizes benzodiazepine reinforcement in animal models, produces dysphoria in normal subjects, and has had no reported abuse in foreign marketing.

Although **MAZICON** has a benzodiazepine-like structure it does not act as a benzodiazepine agonist in man and is not a controlled substance.

OVERDOSAGE: Large intravenous doses of **MAZICON**, when administered to healthy normal volunteers in the absence of a benzodiazepine agonist, produced no serious adverse reactions, severe signs or symptoms, or clinically significant laboratory test abnormalities. In clinical studies, most adverse reactions to flumazenil were an extension of the pharmacologic effects of the drug in reversing benzodiazepine effects.

Reversal with an excessively high dose of **MAZICON** may produce anxiety, agitation, increased muscle tone, hyperesthesia and possibly convulsions. Convulsions have been treated with barbiturates, benzodiazepines and phenytoin, generally with prompt resolution of the seizures. (See WARNINGS.)

DOSE AND ADMINISTRATION: **MAZICON** is recommended for intravenous use only. It is compatible with 5% dextrose in water, lactated Ringer's and normal saline solutions. If **MAZICON** is drawn into a syringe or mixed with any of these solutions, it should be discarded after 24 hours. For optimum sterility, **MAZICON** should remain in the vial until just before use. As with all parenteral drug products, MAZICON should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

To minimize the likelihood of pain at the injection site, MAZICON should be administered through a freely running intravenous infusion into a large vein.

REVERSAL OF CONSCIOUS SEDATION OR IN GENERAL ANESTHESIA: For the reversal of the sedative effects of benzodiazepines administered for conscious sedation or general anesthesia, the recommended initial dose of **MAZICON** is 0.2 mg (2 mL) administered intravenously over 15 seconds. If the desired level of consciousness is not obtained after waiting an additional 45 seconds, a further dose of 0.2 mg (2 mL) can be injected and repeated at 60-second intervals where necessary (up to a maximum of 4 additional times) to a maximum total dose of 1 mg (10 mL). The dose should be individualized based on the patient's response, with most patients responding to doses of 0.6 to 1 mg. (See INDIVIDUALIZATION OF DOSAGE.)

In the event of resedation, repeated doses may be administered at 20 minute intervals as needed. For repeat treatment, no more than 1 mg (given as 0.2 mg/min) should be administered at any one time, and no more than 3 mg should be given in any one hour.

It is recommended that MAZICON be administered as the series of small injections described (not as a single bolus injection) to allow the practitioner to control the reversal of sedation to the approximate endpoint desired and to minimize the possibility of adverse effects. (See INDIVIDUALIZATION OF DOSAGE.)

MANAGEMENT OF SUSPECTED BENZODIAZEPINE OVERDOSE: For initial management of a known or suspected benzodiazepine overdose, the recommended initial dose of **MAZICON** is 0.2 mg (2 mL) administered intravenously over 30 seconds. If the desired level of consciousness is not obtained after waiting 30 seconds, a further dose of 0.3 mg (3 mL) can be administered over another 30 seconds. Further doses of 0.5 mg (5 mL) can be administered over 30 seconds at 1-minute intervals up to a cumulative dose of 3 mg.

Do not rush the administration of **MAZICON**. Patients should have a secure airway and intravenous access before administration of the drug and be awakened gradually. (See PRECAUTIONS.)

Most patients with benzodiazepine overdose will respond to a cumulative dose of 1-3 mg of **MAZICON**, and doses beyond 3 mg do not reliably produce additional effects. On rare occasions, patients with a partial response at 3 mg may require additional titration up to a total dose of 5 mg (administered slowly in the same manner).

If a patient has not responded 5 minutes after receiving a cumulative dose of 5 mg **MAZICON**, the major cause of sedation is likely not to be due to benzodiazepines, and additional **MAZICON** is likely to have no effect.

In the event of resedation, repeated doses may be given at 20-minute intervals if needed. For repeat treatment, no more than 1 mg (given as 0.5 mg/min) should be given at any one time and no more than 3 mg should be given in any one hour.

SAFETY AND HANDLING: **MAZICON** is supplied in sealed dosage forms and poses no known risk to the health care provider. Routine care should be taken to avoid aerosol generation when preparing syringes for injection, and spilled medication should be rinsed from the skin with cool water.

HOW SUPPLIED: 5 mL multiple-use vials containing 0.1 mg/mL flumazenil:
Boxes of 10 (NDC 0004-6904-14).
10 mL multiple-use vials containing 0.1 mg/mL flumazenil:
Boxes of 10 (NDC 0004-6905-14).
Store at 59° to 86° F (15° to 30° C).

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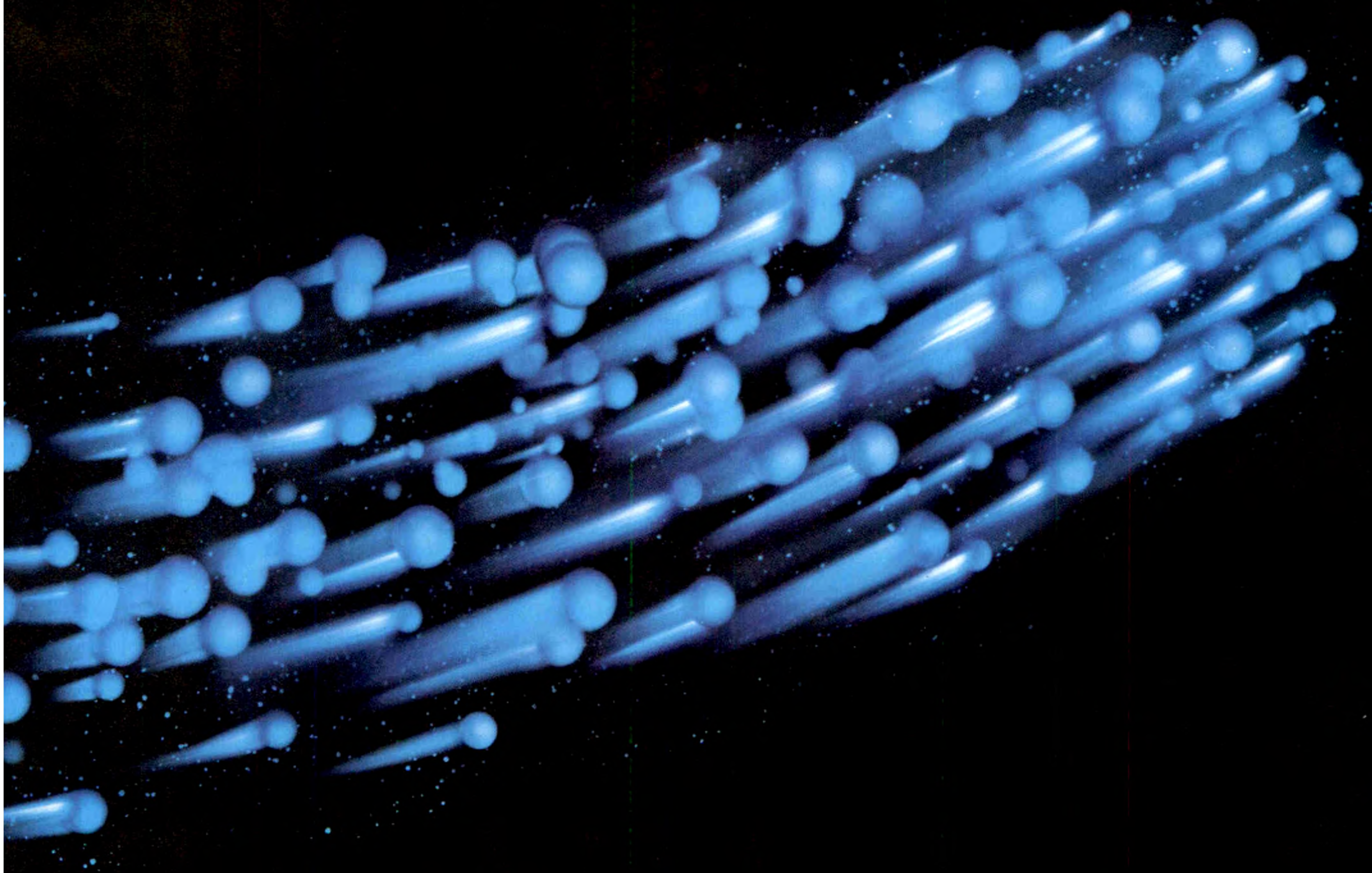

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Free Polymerized Hemoglobin Versus Hydroxyethyl Starch in Resuscitation of Hypovolemic Dogs

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Polymerized bovine hemoglobin (PBH) was compared with hydroxyethyl starch (HES) in a hypovolemic shock model. Eighteen dogs were subjected to hemorrhage; systolic arterial blood pressure was maintained at 40 mm Hg for 30 min (mean blood pressure 37.8 ± 4.7 [SD] mm Hg). Resuscitation was conducted by infusing their own shed blood (control group) or 6% HES (mol wt 200,000) in 0.9% NaCl (HES group) or PBH (PBH group), both in an equal amount to the shed blood. Directly after infusion, oxygen delivery and consumption returned to prehemorrhage levels in all three groups. In the HES group, the lowered arterial oxygen content was compensated by a 158% increase in cardiac output, in contrast to an increase of 31% and 9%, respectively, in the control and PBH groups. Early recovery from hypovolemic shock with regard to oxygen transport and delivery in the PBH group seemed to be comparable to the control group, without the increase in cardiac output seen with HES infusion.

(Anesth Analg 1992;75:811–7)

Instantaneous restoration of (micro)circulation and (tissue)oxygenation is essential for the outcome of hypovolemic shock (1–3). The ideal fluid would be directly available in large amounts, would preferably exert colloid osmotic pressure, would possess oxygen transport capacity, and would have no serious side effects. Human hemoglobin solutions (whole blood or packed cells, or both) are limited in quantity (shortage of donors), are not immediately available (time-consuming blood group determinations or cross-matching procedures, or both), and still present some serious side effects (e.g., infections). The most frequently advocated colloid solutions, such as dextran and hydroxyethyl starch (HES), whether or not in combination with hyperosmotic solutions, fulfill many of these demands, except for oxygen transport capacity. Although there is rapid improvement in hemodynamic status after administration of these solutions, oxygen utilization during anemia is predominantly limited by oxygen supply—total volume available to the tissues per unit time (4). In 1934, the first attempts were made to use a solution containing free hemoglobin (5). Hypercoagulability and renal failure were caused by red cell stroma (6). Rabiner and coworkers (7) described a purifying method that resulted in almost complete clearance of the erythrocyte debris ("stroma-free hemoglobin"). Polymerization of the hemoglobin tetramer prolonged its intravascular persistence, increased its half-life, and reduced its colloid osmotic pressure (8,9). However, none of the previously described solutions have been clinically accepted (10–12).

Because there are limitations with the use of human blood, as mentioned earlier, other mammalian sources of hemoglobin have been sought. Polymerized bovine hemoglobin (PBH) consists of an ultrapurified polymerized hemoglobin solution of bovine origin. An important difference between human and bovine hemoglobin is found in the regulation of oxygen affinity: bovine hemoglobin is controlled by chloride ions rather than by 2,3-diphosphoglycerate (2,3-DPG) (13,14). The P_{50} (Po_2 required for 50% saturation with O_2) of the oxygen dissociation curve of PBH under standard conditions (pH 7.4, Pco_2 40 mm Hg, 37°C) is 17–23 mm Hg (B. Braun Melsungen AG: Wissenstand Hemopure I, Stand: März 1990). Bovine hemoglobin also shows a more pronounced Bohr effect (15), resulting in an enhanced oxygen delivery in regions characterized by low pH or elevated Pco_2, or both. Endotoxin and phospholipid levels are lower than those in earlier preparations (16). Vlahakes et al. (16) previously demonstrated in a

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blood exchange model that this PBH solution is capable of oxygen and carbon dioxide transport.

The objectives in these experiments were twofold: first, to observe the immediate effects of PBH as an oxygen-carrying resuscitation fluid under conditions of severe hypovolemia and subsequent normovolemia; second, to study the medium-term effects (7 days) of a large-volume infusion of stroma-free hemoglobin after hypovolemic shock.

Methods

The study protocol was approved by our institutional animal investigation committee; the experiments were performed according to the institutional standards for laboratory animal care. A total of 18 male and female mongrel dogs (mean body wt 17.33 ± 3.86 [SD] kg) were randomly assigned to one of three groups. After premedication with fluanison (0.1 mg/kg IM) and fentanyl (0.02 mg/kg IM), they were anesthetized by sodium pentobarbital (20–25 mg/kg IV). The trachea was intubated, and ventilation with an air/oxygen mixture (inspired O_2 concentration 0.4) was controlled to maintain CO_2 tension between 38 and 42 mm Hg, as assessed by the continuous measurement of end-tidal CO_2 concentration. A catheter was inserted into the femoral artery for direct measurement of arterial pressure and for withdrawal of blood. A balloon-tipped, flow-directed, pulmonary artery thermodilution catheter was introduced through the jugular vein to the pulmonary artery for measurement of pulmonary artery pressure, pulmonary capillary wedge pressure, and cardiac output, using a thermodilution technique. An additional catheter was introduced in a peripheral vein for administration of fluids (3 $mL \cdot kg^{-1} \cdot h^{-1}$, lactated Ringer's solution). After catheterization, the animals were heparinized by an intravenous single bolus injection of 250 IU/kg.

The arterial and venous blood samples were simultaneously and anaerobically collected. Blood gas analysis was performed immediately. The blood samples were further analyzed for hemoglobin, hematocrit, sodium, potassium, protein, calcium, urea, creatinine, magnesium, glutamate oxaloacetate transaminase (GOT), glutamate pyruvate transaminase (GPT), creatine kinase (CK), lactate dehydrogenase, and osmolality. The red color of plasma containing free hemoglobin could cause a disturbance of clinicochemical test procedures based on optical density measurement. An additional set of plasma samples was screened for free hemoglobin content. If free hemoglobin was present in the plasma, a precipitation step (using zinc) was performed, and subsequent centrifugation left the supernatant with a rest concentration of hemoglobin ≤0.5 g/dL (B. Braun Melsungen AG). This supernatant was again analyzed for the above-mentioned variables. Urine was collected for quantity, creatinine, and urea measurement.

Table 1. Characteristics of Ultrapurified Polymerized Bovine Hemoglobin as Stated by the Manufacturer[a]

Hemoglobin concentration	11 ± 2 g/100 mL
Methemoglobin content	<10%
Polymerized fraction	50%–60%
Molecular size	68,000–500,000 daltons
Colloid oncotic pressure	±20 mm Hg
Sodium content	120 ± 20 mmol/L
Potassium content	4.0 ± 1 mmol/L
Chloride content	115 ± 25 mmol/L
pH	7.8 ± 0.4
Osmolarity	250 ± 40 mOsm/kg
P_{50}	17–23 mm Hg
Endotoxin content[b]	<0.5 EU/mL
Phospholipid content[b]	1 nmol/mL

P_{50}, Po_2 required for 50% saturation with O_2; EU, endotoxin units.
Mean ± SD.
[a] B. Braun Melsungen AG.
[b] Vlahakes et al. (16).

Cardiac output was calculated by a cardiac output computer (model 78231D, Hewlett Packard). Using 10 mL of an iced 5% dextrose in water solution, the mean of at least three sequential cardiac output measurements with a coefficient of variation <10% was taken as a representative value. For the calculation of arterial and venous oxygen content, the dissolved oxygen is added to the hemoglobin-bound oxygen by using the measured Po_2 and the solubility coefficient of 0.0031 mL of oxygen/dL/mm Hg Po_2. In the PBH group, oxygen content was calculated using the total hemoglobin (native and bovine) amount. Pressures were recorded on a four-channel writer.

After stabilization, blood samples and baseline values of hemodynamic variables were obtained. Within 15–20 min, the dogs were bled sufficiently to maintain a systolic arterial pressure of 40 mm Hg. This pressure was sustained for a 30-min period by further withdrawal or reinfusion of blood. At the end of this 30-min period, blood samples were taken and hemodynamics measured. The first group was resuscitated with their own shed blood (control group); the second group received 6% HES (mol wt 200,000) in 0.9% NaCl (B. Braun Melsungen AG) (HES group); the third group received bovine stroma-free hemoglobin (PBH, units of approximately 120 mL; composition is listed in Table 1 [B. Braun Melsungen AG]) (PBH group); the HES and PBH groups each received an amount equal to the shed blood. All solutions were administered over a 15–20-min period and infused at ±37°C. On completion of the infusion, a 30-min stabilization period followed, after which another series of measurements and blood collection was performed. At the end of the experiment, the

Table 2. Hemodynamic Variables During and After the Hypovolemic Shock Experiment in the Three Study Groups

	Baseline	Shock	Resuscitation	Day 7
Heart rate (bpm)				
CTR	57.3 ± 8.7	209.3 ± 39.6	75.0 ± 23.3	58.0 ± 9.0
HES	74.7 ± 32.2	186.8 ± 14.6	107.0 ± 19.9^{a,b}	66.0 ± 7.6
PBH	60.0 ± 8.5	188.3 ± 23.1	65.0 ± 13.4	74.0 ± 20.3
ABP sys (mm Hg)				
CTR	95.8 ± 15.3	46.0 ± 8.3	102.5 ± 8.8	90.8 ± 4.9
HES	85.8 ± 17.7	40.3 ± 4.5	101.7 ± 16.3	84.2 ± 3.8
PBH	84.2 ± 8.0	40.2 ± 4.1	111.7 ± 4.1	80.0 ± 4.5
ABP dia (mm Hg)				
CTR	61.7 ± 15.1	38.8 ± 4.9	71.7 ± 11.2	52.5 ± 5.2
HES	56.7 ± 18.6	34.2 ± 6.6	68.3 ± 11.7	50.8 ± 6.6
PBH	53.8 ± 10.3	34.2 ± 2.0	73.3 ± 15.4	43.2 ± 4.9^{c}
ABP mean (mm Hg)				
CTR	73.1 ± 14.6	41.2 ± 6.0	81.9 ± 9.5	65.3 ± 4.5
HES	66.4 ± 17.9	36.2 ± 5.8	79.4 ± 12.4	61.9 ± 5.5
PBH	63.9 ± 6.7	36.1 ± 2.5	86.1 ± 11.0	55.4 ± 4.6^{c}
PAP sys (mm Hg)				
CTR	17.0 ± 2.4	5.7 ± 2.9	10.0 ± 2.8	12.8 ± 3.2
HES	12.3 ± 3.8^{a}	5.5 ± 2.2	13.7 ± 4.3	13.7 ± 4.4
PBH	13.7 ± 2.7	4.7 ± 2.1	15.5 ± 3.6	13.3 ± 1.5
PAP dia (mm Hg)				
CTR	6.7 ± 2.1	NS	6.7 ± 3.0	5.5 ± 2.0
HES	5.0 ± 2.1	NS	6.0 ± 2.8	5.0 ± 1.7
PBH	5.8 ± 2.2	NS	7.2 ± 2.6	5.3 ± 1.5
PCWP (mm Hg)				
CTR	5.7 ± 2.6	2.3 ± 2.4	5.5 ± 3.2	4.5 ± 2.3
HES	4.0 ± 1.9	1.5 ± 0.5	3.5 ± 1.8	3.8 ± 1.3
PBH	4.0 ± 1.9	1.5 ± 2.0	6.5 ± 1.4	4.2 ± 2.6
CVP (mm Hg)				
CTR	4.7 ± 2.9	−0.7 ± 1.2	3.5 ± 3.7	3.7 ± 3.7
HES	1.7 ± 1.5^{a}	−1.0 ± 1.8	1.5 ± 2.5	2.7 ± 2.1
PBH	2.3 ± 1.4	−2.3 ± 1.4	4.0 ± 0.8	3.3 ± 2.0
Mean CO ($mL \cdot min^{-1} \cdot kg^{-1}$)				
CTR	95.3 ± 23.1	71.0 ± 7.8	125.0 ± 21.8	95.5 ± 11.6
HES	85.3 ± 24.0	57.0 ± 8.5^{a}	219.7 ± 96.2^{a,b}	116.4 ± 22.8
PBH	92.5 ± 21.6	62.6 ± 9.8	100.7 ± 18.1	137.9 ± 65.1
Cao$_2$ (mL/dL)				
CTR	16.6 ± 2.6	17.7 ± 1.8	16.9 ± 2.5	13.6 ± 1.8
HES	17.6 ± 2.1	18.4 ± 1.5	11.7 ± 1.8^{a,b}	14.9 ± 1.5
PBH	19.4 ± 1.2	19.4 ± 0.7	16.6 ± 0.5	13.4 ± 2.6
Cvo$_2$ (mL/dL)				
CTR	12.1 ± 2.6	9.5 ± 1.7	13.0 ± 2.4	10.1 ± 1.2
HES	13.3 ± 1.6^{c}	9.6 ± 3.1	8.8 ± 1.5^{a,b}	11.0 ± 1.3
PBH	15.8 ± 1.9	11.9 ± 2.2	12.6 ± 1.2	8.9 ± 3.0
Svo$_2$ (%)				
CTR	74.8 ± 5.1	55.8 ± 7.1	81.4 ± 5.1	78.0 ± 7.1
HES	80.4 ± 9.4	55.1 ± 18.4	83.8 ± 3.9	78.7 ± 5.9
PBH	85.9 ± 7.8	64.0 ± 11.5	81.5 ± 8.6	71.5 ± 18.2
Do$_2$ ($mL \cdot min^{-1} \cdot kg^{-1}$)				
CTR	16.1 ± 5.9	12.5 ± 1.5	21.1 ± 5.0	13.0 ± 2.5
HES	14.8 ± 3.4	10.5 ± 2.2	26.4 ± 14.8	17.3 ± 3.6
PBH	18.0 ± 4.9	12.2 ± 2.2	16.8 ± 3.4	18.4 ± 9.0
Vo$_2$ ($mL \cdot min^{-1} \cdot kg^{-1}$)				
CTR	4.2 ± 0.8	5.8 ± 1.1	4.9 ± 0.6	3.4 ± 1.0
HES	3.5 ± 0.7	4.9 ± 2.1	6.5 ± 3.4	4.5 ± 1.1
PBH	3.1 ± 0.4^{c}	4.6 ± 0.8	4.0 ± 0.7	5.7 ± 2.9
O$_{2\text{ER}}$ (%)				
CTR	27.7 ± 5.6	46.1 ± 6.9	23.7 ± 3.9	25.8 ± 5.5
HES	24.5 ± 7.3	47.3 ± 17.0	25.0 ± 1.7	25.9 ± 4.5
PBH	18.5 ± 6.7	38.7 ± 11.2	24.5 ± 6.7	33.2 ± 17.5

CTR, control group; HES, hydroxyethyl starch group; PBH, polymerized bovine hemoglobin group; ABP sys, systolic arterial blood pressure; ABP dia, diastolic arterial blood pressure; ABP mean, mean arterial blood pressure; PAP sys, systolic pulmonary artery pressure; PAP dia, diastolic pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; CVP, central venous pressure; mean CO, mean cardiac output; Cao$_2$, arterial oxygen content; Cvo$_2$, mixed venous oxygen content; Svo$_2$, mixed venous oxygen saturation; Do$_2$, oxygen supply; Vo$_2$, oxygen consumption; O$_{2\text{ER}}$, oxygen extraction ratio; NS, not different from PAP sys.

Mean ± SD.

[a] Significant difference between control and HES.

[b] Significant difference between HES and PBH.

[c] Significant difference between control and PBH.

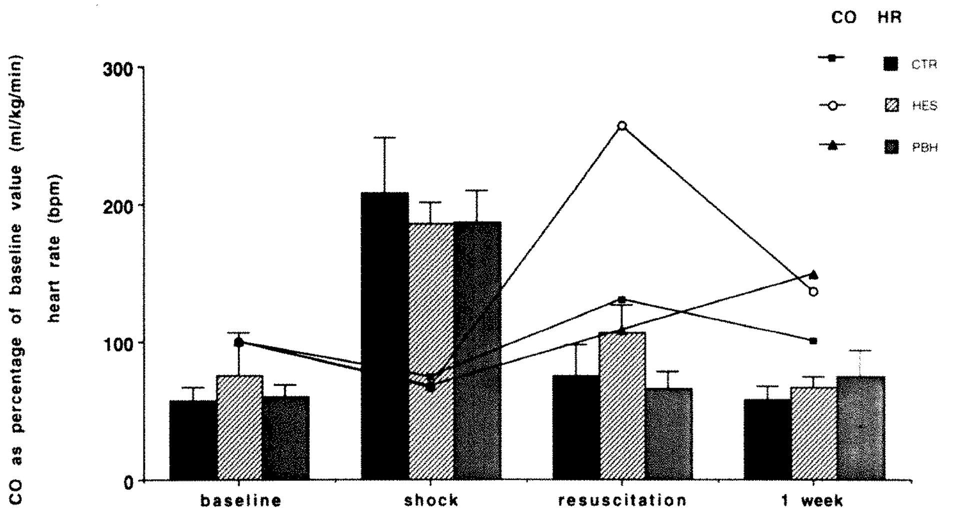

Figure 1. Changes in cardiac output (as % of baseline value) and heart rate throughout the hypovolemic shock experiment. bpm, beats/min.

tracheas were extubated and the animals transported to the animal care facility.

At approximately 24, 48, and 72 h after the end of the shock phase, 24-h urine and blood samples were obtained. At day 7, the animals were again anesthetized and ventilated, hemodynamic variables were measured, and blood samples were taken (same procedures and blood analysis as day 1). Finally, the animals were killed, and biopsy specimens of the left ventricle, lungs, liver, spleen, and kidney were sent for histologic examination.

Results are expressed as mean ± SD. Statistical analyses were performed using analysis of variance for a two-factor repeated measures or the paired Student's *t*-test where appropriate. A *P* value <0.05 was considered significant.

Results

All animals survived the 7-day period. The mean weight loss over this period was 1.12 (±0.93) kg in the control and PBH groups and 1.63 (±1.02) kg in the HES group (difference not significant). The mean volume of shed blood amounted to 30.85 (±6.11) mL/kg. None of the dogs showed adverse reactions on infusion of the fluids.

The hemodynamic variables changed to a similar extent in the three groups during the shock period; heart rate increased and cardiac output and central filling pressures decreased (Table 2). After resuscitation, heart rate in the HES group remained significantly elevated ($P < 0.05$) compared with the control and PBH groups (Figure 1). Cardiac output in the control and the PBH groups increased to values slightly above prehemorrhage levels (respectively, 131% and 109% of baseline values), whereas in the HES group, it peaked to 258% of baseline value ($P < 0.05$; Figure 1). Arterial and venous oxygen content were both depressed in the HES group after resuscitation ($P < 0.05$), whereas in the PBH group, values comparable to the control group were found. Oxygen delivery, consumption, and extraction ratio showed no significant difference among the three groups.

Hemoglobin content decreased to 62% of baseline value in the HES group after infusion (Table 3); hematocrit decreased to 56% and 62% in PBH and HES groups, respectively (Figure 2). Both hemoglobin and hematocrit returned to near-normal values at day 1. The plasma creatinine values were equally increased in the three groups on the first day. Diuresis during the first 24 h was significantly increased in the PBH group, whereas the other two groups showed a decrease. Creatinine clearance during this period was less in the HES group compared with the control and PBH groups. No significant differences were found in serum sodium, potassium, chloride, urea, magnesium, and osmolality over the course of the experiment. Total blood protein and calcium content was less in the HES group after infusion (for protein even up to the third day). The CK, GOT, GPT, and lactate dehydrogenase values all increased after the shock period; CK, GOT, and GPT were more pronounced in the PBH group. Even after precipitation of the free hemoglobin, GOT and CK remained significantly increased compared with the HES group.

One dog (in the control group) had a subendocardial infarction. Further histologic examination produced no abnormalities in heart, lungs, or kidneys. Some aspecific vascular congestion was observed in

Table 3. Biochemical Results, Diuresis, and Creatinine Clearance During and After the Hypovolemic Shock Experiment in the Three Study Groups

	Baseline	Shock	Resuscitation	Day 1	Day 2	Day 3	Day 7
Hemoglobin (g/dL)							
CTR	11.4 ± 1.8	12.3 ± 1.2	11.4 ± 2.0	12.5 ± 2.2	12.8 ± 1.7	11.7 ± 2.2	9.5 ± 1.3
HES	12.2 ± 1.7	12.9 ± 1.0	7.6 ± 1.3[a,b]	11.9 ± 1.7	11.4 ± 1.4	11.3 ± 2.1	9.9 ± 1.1
PBH	13.5 ± 0.8	13.7 ± 0.4[c]	11.4 ± 0.4	13.3 ± 1.3	13.2 ± 1.8	12.8 ± 1.7	9.2 ± 1.7
Free hemoglobin (g/dL)							
PBH	0	0	5.1 ± 0.5	2.7 ± 0.6	1.5 ± 0.3	0.6 ± 0.2	0
Hematocrit (L/L)							
CTR	34.6 ± 5.0	37.6 ± 2.7	34.4 ± 4.4	36.8 ± 7.1	40.2 ± 4.3	34.2 ± 7.2	29.5 ± 2.1
HES	37.0 ± 6.6	39.8 ± 3.9	22.8 ± 2.5[a]	37.5 ± 7.0	34.3 ± 4.8	33.3 ± 5.3	29.4 ± 2.7
PBH	39.0 ± 3.0	40.7 ± 1.7	22.0 ± 2.7[c]	37.2 ± 5.8	36.7 ± 5.8	37.8 ± 4.5	27.7 ± 4.2
Creatinine (mg/dL)							
CTR	0.74 ± 0.39	1.31 ± 0.16	1.11 ± 0.21	0.90 ± 0.07	0.89 ± 0.09	0.81 ± 0.1	0.89 ± 0.14
HES	1.05 ± 0.25	1.31 ± 0.27	1.13 ± 0.32	0.81 ± 0.29	0.89 ± 0.19	0.88 ± 0.16	0.98 ± 0.18
PBH	0.88 ± 0.07	1.19 ± 0.09	0.96 ± 0.05	0.80 ± 0.07	0.87 ± 0.13	0.82 ± 0.18	0.85 ± 0.22
Urea (mg/dL)							
CTR	14.0 ± 3.7	17.6 ± 4.4	16.0 ± 4.9	17.4 ± 8.9	14.5 ± 5.7	14.2 ± 4.3	12.4 ± 3.6
HES	16.7 ± 2.7	19.2 ± 2.5	17.8 ± 3.2	12.3 ± 7.1	11.2 ± 3.3	15.0 ± 2.6	16.0 ± 6.0
PBH[d]	12.3 ± 1.7[b]	15.0 ± 2.6	11.3 ± 2.2[b]	12.7 ± 2.9	13.5 ± 1.4	11.8 ± 3.0	12.5 ± 2.2
GOT (U/L) (N 10–40 U/L)							
CTR	44.6 ± 54.9	42.6 ± 45.8	46.2 ± 49.3	179.4 ± 193.1	102.5 ± 121.1	47.8 ± 40.3	16.0 ± 7.6
HES	15.5 ± 4.1	18.2 ± 7.5	12.7 ± 5.2	128.0 ± 77.9	41.7 ± 22.6	18.3 ± 4.3	12.6 ± 5.5
PBH[d]	17.3 ± 8.9	23.2 ± 16.1	12.8 ± 11.6	634.2 ± 497.6[b]	257.3 ± 149.7[b]	6.5 ± 30.9[b]	12.7 ± 8.2
GPT (U/L) (N 10–40 U/L)							
CTR	38.0 ± 49.2	34.8 ± 45.3	38.2 ± 49.4	68.2 ± 96.5	93.0 ± 100.8	75.8 ± 74.0	58.2 ± 66.9
HES	20.5 ± 7.8	19.0 ± 6.8	12.5 ± 4.0	43.0 ± 18.3	40.2 ± 10.5	34.0 ± 7.3	21.5 ± 6.5[a]
PBH	17.5 ± 6.1	16.5 ± 5.5	14.0 ± 2.0	350.5 ± 714.8	316.7 ± 487.4	250.6 ± 338.3	54.3 ± 66.7
LDH (U/L)							
CTR	72 ± 35	103 ± 66	118 ± 74	158 ± 110	174 ± 118	114 ± 38	54 ± 16
HES	64 ± 26	80 ± 36	57 ± 36	137 ± 46	71 ± 37	87 ± 34	53 ± 14
PBH[d]	61 ± 32	89 ± 43	115 ± 133	199 ± 153	85 ± 48	139 ± 118	90 ± 59
CK (U/L)							
CTR	393 ± 442	442 ± 407	493 ± 447	2385 ± 2102	912 ± 1117	403 ± 374	116 ± 33
HES	152 ± 88	201 ± 137	132 ± 67	1237 ± 996	254 ± 169	116 ± 64	106 ± 115
PBH[d]	143 ± 76	259 ± 200	185 ± 148	3899 ± 1408[b]	1977 ± 680[b]	787 ± 284[b]	108 ± 111
Diuresis (mL/h)							
CTR	12.2 ± 6.3	[e]	[e]	7.9 ± 1.8	11.4 ± 7.5	12.8 ± 10.9	10.3 ± 8.0
HES	13.8 ± 6.0	[e]	[e]	4.1 ± 3.8	17.7 ± 19.8	21.3 ± 8.6	10.0 ± 6.4
PBH	6.9 ± 3.5	[e]	[e]	18.2 ± 10.2[b]	15.9 ± 9.2	9.4 ± 2.5[b]	11.7 ± 9.7
Creatinine clearance (mL/min)							
CTR	60.2 ± 57.4	[e]	[e]	30.0 ± 15.7	42.1 ± 7.2	59.0 ± 41.1	41.3 ± 26.6
HES	32.6 ± 17.8	[e]	[e]	6.1 ± 8.0[a,b]	38.7 ± 35.7	55.2 ± 20.7	29.0 ± 11.2
PBH	40.1 ± 21.0	[e]	[e]	35.3 ± 8.5	41.6 ± 17.8	32.1 ± 8.3	36.7 ± 11.5

CTR, control group; HES, hydroxyethyl starch group; PBH, polymerized bovine hemoglobin group; GOT, glutamate oxaloacetate transaminase; GPT, glutamate pyruvate transaminase; LDH, lactate dehydrogenase; CK, creatine kinase.

Mean ± SD.

[a] Significant difference between control and HES.

[b] Significant difference between HES and PBH.

[c] Significant difference between control and PBH.

[d] Values for the PBH group refer to plasma after precipitation of free hemoglobin.

[e] Incorporated in 24-h collection.

the liver biopsies in all three groups. The same was true for iron deposits in the spleen: limited in quantity and no evident preference for one of the groups.

Discussion

The goal of resuscitation should be the restoration of normal tissue oxygenation (3), as defined by oxygen

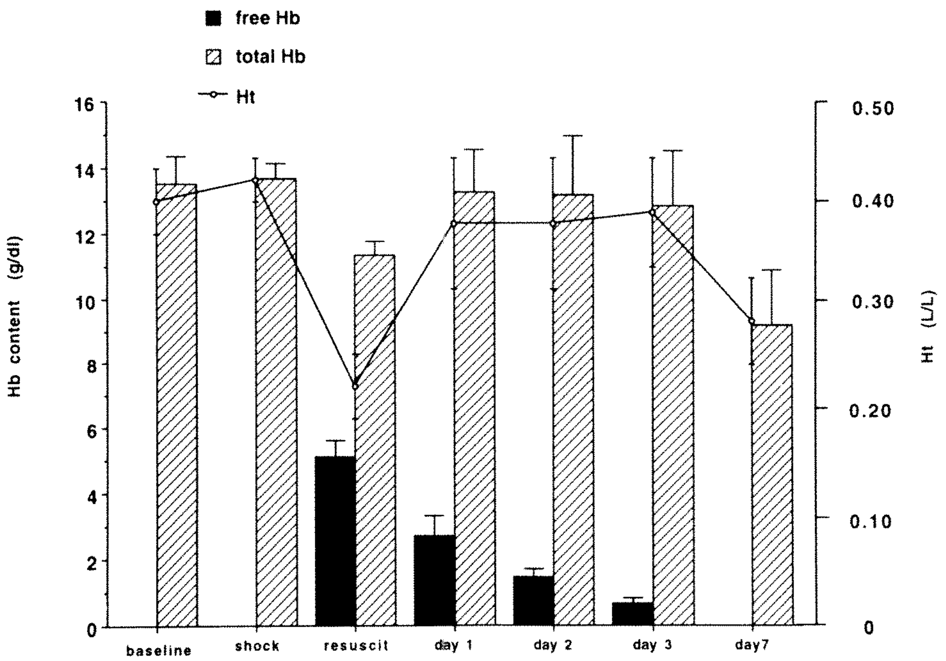

Figure 2. Free and erythrocytic hemoglobin (Hb) content and hematocrit (Ht) in the PBH group (mean ± SD). resuscit, resuscitation.

delivery and consumption. Sufficient oxygen supply can only be achieved by increasing heart rate and cardiac output when non-oxygen-carrying solutions (e.g., dextran, HES) are infused. Oxygen content in the PBH group was calculated using the total hemoglobin (native and bovine) amount. Vlahakes et al. (16) demonstrated in sheep that the oxygen transport capability of PBH is nearly identical to that of native hemoglobin, supported by an almost linear correlation between PBH contribution to oxygen content and declining hematocrit. Oxygen supply in our HES and PBH groups was equal to the control group. In the HES group, the lower arterial oxygen content was compensated by a 158% increase in cardiac output. However, when healthy animals are exposed to a hematocrit of <6%–10%, oxygen delivery and mixed venous P_{O_2} decrease precipitously, resulting in death (3,17,18). Despite a significant decrease in mixed venous oxygen content in the HES-group animals, the oxygen extraction ratio showed no difference among the three groups.

Gould et al. (19) showed that an adequate hemoglobin content is far more important to tissue oxygenation than a high P_{50}. Oxygen delivery is further dependent on diffusion distance (4). The effect of dextran on microcirculation has been well described (20–22); the reduced red cell sludging and platelet and leukocyte adhesiveness are probably due to hemodilution or coating of these cells, or both, resulting in enhanced tissue perfusion (23,24). A free hemoglobin solution should theoretically present a similar "hemodiluting" effect. Hauser and Shoemaker (3) demonstrated a lowered viscosity after crystalline hemoglobin infusion. However, systemic vascular resistance did not decrease. Further investigation into this presumed "dextran effect" of stroma-free hemoglobin seems appropriate.

Hemoglobin is removed from the circulation in two principal ways: (a) complex formation with haptoglobin and consequent absorption of this complex by the reticuloendothelial system; and (b) dissociation of the free hemoglobin in monomers and dimers, followed by glomerular filtration (12). Although we measured high levels of GOT, GPT, and CK in the PBH group, there was no histologic evidence of any damage to the liver. The reversible increase of these enzymes during the first 3 days was possibly due to an interference between the photometric assay and the hemoglobin rest concentration after the precipitation process. Although some increase in enzyme levels might be attributed to this interference, the rest concentration of free hemoglobin of ≤0.5 g/dL is too low to be solely responsible. The increase in GOT, GPT, and CK in the PBH group probably reflects a limited, transient dysfunction of the liver, presumably induced by a flooded reticuloendothelial system.

After infusion of 32.07 ± 4.94 mL/kg of PBH, renal toxicity could not be found in our experiment. A significant increase in urine production during the first 24 h is probably due to osmotic diuresis, caused by hemoglobinuria of monomers and dimers. Using stroma-free hemoglobin in rats, Lee et al. (25) demonstrated that no apparent depression of kidney function is to be expected until an equivalent dose of 150% of circulating blood volume is reached (±75 mL/kg). This reversible toxicity could be diminished by adding bicarbonate. In an exchange transfusion model (≥95% exchange of blood volume by PBH), Vlahakes et al. (16) found only a slight increase in blood urea nitrogen and creatinine on the second day, with return to baseline level at day 3. The mechanism of the transient renal toxicity is still unclear but probably results either from some direct toxic effect of hemoglobin on tubular epithelium or from intratubular precipitation and consequent obstruction (10,12,23).

Both in the HES and the PBH groups, hematocrit and (erythrocytic) hemoglobin returned to prehemorrhage levels within 24 h (Table 2, Figure 2). This rapid recovery is presumably the result of using nonsplenectomized dogs.

The favorable results of stroma-free hemoglobin obtained in this study are in contrast to the data presented by Dawidson et al. (26). In their ischemic intestinal shock model, 6 of 8 rats transfused with stroma-free hemoglobin died within 24 h, whereas 15 of 16 rats infused with either lactated Ringer's solution or 3% albumin in lactated Ringer's solution survived for 7 days. Proposed explanations for the failure of stroma-free hemoglobin are (a) diminished volume expansion compared with the other two fluids, and (b) an increased vascular permeability, possibly due to enhanced production of free radicals. However, when the objective of resuscitation is to optimize tissue perfusion and oxygenation, the infusion of 300 mL/kg stroma-free hemoglobin will result in an enormous increase in hemoglobin content and a concomitant decrease in viscosity. The authors only present hematocrit, without mentioning hemoglobin content. The experiment would have been more realistic if oxygen transport capacities had been the goal of resuscitation.

In conclusion, ultrapurified PBH restored oxygen delivery and consumption after hemorrhagic shock in the same way as infusion with autologous blood. The limited degree of hemorrhage enabled the animals in the HES group to restore oxygen delivery by increasing their cardiac output up to 158% above baseline value. Besides a transient increase in liver enzymes, no apparent organ dysfunction was noticeable after PBH infusion during a 7-day follow-up or at autopsy.

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CASE REPORTS

Profound Hemodilution: What Is the Critical Level of Hemodilution at Which Oxygen Delivery-Dependent Oxygen Consumption Starts in an Anesthetized Human?

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The risks of homologous blood transfusion are well known, and some patients may refuse blood transfusions on religious grounds. Transfusion requirements may be diminished by hemodilution techniques. The critical level of hemodilution in humans, defined as the point at which oxygen consumption (Vo_2) starts to decrease because of insufficient oxygen delivery (Do_2), is not known. With permission of the family, the case history of a Jehovah's Witness patient with a critical level of hemodilution and Do_2-dependent Vo_2, due to excessive blood loss during surgery, is presented.

Case Report

An otherwise healthy 84-yr-old, 60-kg, male Jehovah's Witness had bleeding from the stomach. At admission, the bleeding stopped spontaneously with a hemoglobin concentration of 7.7 g/dL. Examination revealed a malignant tumor of the stomach. Five weeks after admission, the hemoglobin concentration was 10.1 g/dL (hematocrit 31%). Because of the danger of massive and lethal bleeding from the ulcerative tumor, it was decided to perform a total gastrectomy. The patient refused homologous blood products and any form of autologous transfusion. Fully informed consent was obtained for invasive monitoring and for the use of the technique of acute hypervolemic hemodilution (1,2). Because of adhesions between the stomach and spleen, the spleen ruptured during surgery and mobilization of the stomach and massive bleeding followed. At the end of surgery, blood loss was 4500 mL. Twelve hours postoperatively, the patient died. In accordance with medicoethical law in The Netherlands, it was forbidden in this case to administer any blood transfusion.

We now describe the methods and results of our investigations during this case. On the day of surgery, two intravenous cannulas were inserted. The radial artery was cannulated and a thermodilution catheter introduced into a pulmonary artery via the internal jugular vein. Midazolam (2.5 mg IV) was administered before catheter insertion. Heart rate, mean arterial blood pressure, pulmonary artery pressure, and right atrial pressure were monitored continuously. After 30 min of stable cardiovascular status, baseline cardiovascular values were obtained. In addition, arterial and mixed venous blood samples were obtained for measurements of hemoglobin, hemoglobin oxygen saturation, hematocrit, and analysis of blood gases. Systemic vascular resistance, pulmonary vascular resistance, Do_2, Vo_2, and P_{50} (Po_2 at which hemoglobin is 50% saturated with oxygen) were calculated from these acquired data. The oxygen extraction ratio was calculated by dividing Vo_2 by Do_2. P_{50}, corrected to 37°C and pH = 7.40, was calculated (and not measured by in vitro biotonometric technique) from a single measurement of venous pH, Po_2, and oxygen saturation of hemoglobin (3). Anesthesia was induced with fentanyl (5 μg/kg IV), thiopental (5 mg/kg IV), and pancuronium (0.1 mg/kg IV). After tracheal intubation, the lungs were ventilated with 70% nitrous oxide in oxygen, and tidal volume was adjusted to achieve normocapnia. Anesthesia was maintained with fentanyl and enflurane (end-tidal 0.4 vol% throughout the whole surgical procedure) and muscle relaxation maintained with pancuronium (2 mg/h). The bladder was catheterized. Before surgery began, hypervolemic hemodilution was undertaken in three equal steps. Per step, 500 mL of dextran 40 (50 g/L) and 500 mL of lactated Ringer's solution were infused over 10 min. All measurements were repeated after each step. The same variables were recorded after 1500- and 3500-mL blood loss. Peroperatively, lactated Ringer's solution was infused in a volume equal to urine output plus 8 $mL \cdot kg^{-1} \cdot h^{-1}$ (to compensate for fluid loss from the wound). Blood loss was replaced by an equal volume of gelatin solution. Measurements were repeated at the end of surgery (blood loss 4500 mL) and at 1, 2, 4, and 8 h thereafter.

Postoperatively, anesthesia was maintained with continuous intravenous midazolam (0.1 $mg \cdot kg^{-1} \cdot h^{-1}$), and muscle relaxation was achieved with pancuronium (2 mg/h).

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Table 1. Systemic Hemodynamic Measurements Before and After Induction of Anesthesia in an 84-Year-Old Male Patient

	HR (beats/min)	MAP (mm Hg)	PAP (mm Hg)	PWP (mm Hg)	CO (L/min)	SVR (dyne·s·cm^{-5})	Hct (%)	Hb (g/dL)
Preinduction	85	103	23	12	4.4	1818	31	10.1
Postinduction	81	66	14	12	3.5	1440	30	9.6
H1	77	71	21	15	5.0	1040	24	7.5
H2	81	76	28	15	5.2	969	21	6.7
H3	84	73	32	16	5.4	844	20	6.1
1500-mL blood loss	103	82	35	17	5.3	1072	16	5.0
3500-mL blood loss	95	70	31	17	5.5	887	10	3.4
ES	92	56	24	15	5.8	648	9	2.6
1 h postop	117	89	22	5	5.7	1179	12	2.7
2 h postop	104	80	25	10	5.0	1120	12	3.0
4 h postop	92	58	26	13	4.5	800	9	2.6
8 h postop	105	47	25	15	3.8	653	8	1.8

HR, heart rate; MAP, mean arterial pressure; PAP, mean pulmonary artery pressure; PWP, pulmonary wedge pressure; CO, cardiac output; SVR, systemic vascular resistance; Hct, hematocrit; Hb, hemoglobin; H1, H2, H3, data for each step of hypervolemic hemodilution; ES, end of surgery; postop, postoperative.

Table 2. Systemic Oxygenation Before and After Induction of Anesthesia

	Pa_{O_2} (mm Hg)	Pa_{CO_2} (mm Hg)	Pv_{O_2} (mm Hg)	Pv_{CO_2} (mm Hg)	pH art	pH ven	D_{O_2} (L·m^{-2}·min^{-1})	Vo^2 (L·m^{-2}·min^{-1})	ER (%)	P_{50} act (mm Hg)	P_{50} c (mm Hg)
Preinduction	75	37	31	40	7.46	7.44	339	126	37	26.2	27.3
Postinduction	250	36	37	39	7.45	7.43	275	97	35	27.9	29.0
H1	220	35	42	39	7.45	7.42	316	93	30	28.1	29.2
H2	225	36	41	38	7.44	7.41	304	91	30	27.9	28.8
H3	215	36	42	38	7.43	7.40	285	88	31	28.3	29.0
1500-mL blood loss	92	34	33	36	7.40	7.38	218	95	44	28.6	29.1
3500-mL blood loss	170	36	30	39	7.37	7.34	163	86	53	29.3	28.5
ES	226	37	32	39	7.37	7.33	146	75	51	28.7	27.7
1 h postop	230	44	33	46	7.37	7.34	190	90	48	28.7	27.7
2 h postop	262	34	33	40	7.46	7.38	142	68	48	27.5	27.3
4 h postop	293	30	26	38	7.48	7.40	116	73	63	27.5	27.6
8 h postop	345	30	31	38	7.39	7.26	78	53	68	34.6	30.1

Art, arterial; ven, venous; D_{O_2}, oxygen delivery; V_{O_2}, oxygen consumption; ER, oxygen extraction ratio; P_{50} act, P_{O_2} at oxyhemoglobin saturation of 50% measured in mixed venous blood; P_{50} c, P_{50} of mixed venous blood corrected at pH = 7.40 and P_{CO_2} = 40 mm Hg; H1, H2, H3, data for each step of hypervolemic hemodilution; ES, end of surgery; postop, postoperatively.

The lungs were ventilated with 40% oxygen in air, and body temperature was kept normal. Postoperatively, lactated Ringer's solution was infused at 100 mL/h. The critical level of hemodilution was determined from a plot of V_{O_2} against D_{O_2}. The critical point was defined as the point at which V_{O_2} became dependent on D_{O_2} with further hemodilution. To avoid the investigator bias of selecting this point by eye, the critical point was analytically chosen from the intersection of the two best-fit regression lines determined by a least sum of squares technique, as described previously by Schumacker et al. (4).

The resultant hemodynamic data are summarized in Table 1. Stepwise acute hypervolemic hemodilution, with a change in hematocrit from 31% to 20%, resulted in a decrease in systemic vascular resistance of 53% and an increase in cardiac output of 54%. At a hematocrit of 8%, cardiac output was slightly decreased but still maintained compared with the postinduction of anesthesia value before hemodilution was induced. Mean arterial pressure decreased at hematocrit values of <10% because of slightly decreased cardiac output and further decreased systemic vascular resistance. During extreme hemodilution, heart rate increased only slightly.

The results of systemic oxygenation are shown in Table 2. The critical point of D_{O_2} after which V_{O_2} gradually decreased was analytically chosen from the intersection of the two best-fit regression lines (Figure 1). The D_{O_2} at this critical point was 184 mL·m^{-2}·min^{-1} (4.9 mL·kg^{-1}·min^{-1}). The hemoglobin content at this critical point was 4.0 g/dL (Figure 2), with the oxygen extraction ratio 0.44, the mixed venous P_{O_2} 34 mm Hg, and the mixed venous oxyhemoglobin saturation 56%. The position of the oxyhemoglobin dissociation curve (ODC), corrected for changes in pH and P_{CO_2}, shifted to the right, but not before

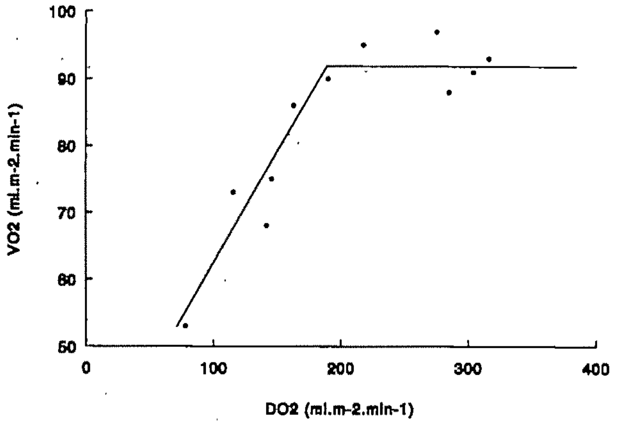

Figure 1. Relationship between oxygen delivery (Do_2) and oxygen consumption (Vo_2) during increasing hemodilution.

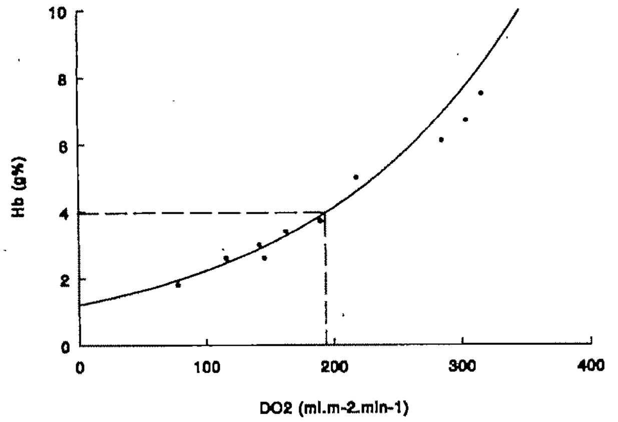

Figure 2. Relationship between oxygen delivery (Do_2) and hemoglobin (Hb) concentration with critical point of Do_2.

hematocrit was 8%. At a hematocrit of 8%, the mixed venous pH decreased, but the arterial pH did not. Twelve hours postoperatively, the patient died at a hemoglobin concentration of 1.6 g/dL.

Discussion

In the present case, values of several variables at the critical point of hemodilution at which Do_2-dependent Vo_2 starts could be recorded. There are no reports in the literature on the systemic oxygenation in humans at such a critical point of hemodilution. The point at which Vo_2 becomes dependent on Do_2 during hemodilution is not established in humans. In our anesthetized patient, Vo_2 started to decline at a Do_2 of 184 $mL \cdot m^{-2} \cdot min^{-1}$ (4.9 $mL \cdot kg^{-1} \cdot min^{-1}$). There are only a few reports concerning critical Do_2 in anesthetized cardiac patients in whom Do_2 was limited, not because of decreased arterial oxygen content but because of decreased cardiac output (5,6). In one study, Vo_2 decreased at Do_2 <330 $mL \cdot m^{-2} \cdot min^{-1}$ and in the other study at Do_2 <300 $mL \cdot m^{-2} \cdot min^{-1}$. The difference in critical Do_2 between our patient and those of the other reports can be easily explained. A decrease in Do_2 by decreased cardiac output of blood with normal hemoglobin content is often accompanied by even more decreased blood flow through the microcirculation, whereas during hemodilution, flows in the microcirculation are accelerated, owing to improved rheologic properties of blood (7). In animal studies, Cain and Chapler (8,9) found a critical Do_2 of 10 $mL \cdot kg^{-1} \cdot min^{-1}$ in anesthetized dogs during anemic hypoxia and when oxygen-supply dependency of Vo_2 started at a hematocrit of 10%. In another study in anesthetized dogs, a critical Do_2 of 7.9 $mL \cdot kg^{-1} \cdot min^{-1}$ was established (10). However, in anesthetized pigs, which are more closely related to humans anatomically and physiologically (11), during hemodilution at a Do_2 of 7.8 $mL \cdot kg^{-1} \cdot min^{-1}$ (the final step of hemodilution in the study protocol), we found that Vo_2 was still well maintained (12). In another pig study, in which the critical Do_2 was not discussed, a critical hemoglobin content (where oxygen supply-dependent Vo_2 started) of 3.9 ± 0.7 g/dL, similar to the present case, was found (13). In other pig studies we also found a critical hemoglobin concentration of 4.0 g/dL (14). In our patient, as in another study using the same anesthesia technique (1), Vo_2 and Do_2 decreased with the induction of anesthesia. Therefore, the values of Do_2 and Vo_2 before induction of anesthesia were not used in Figure 1 to establish the critical point of hemodilution. It is possible that if the patient had been conscious, a different critical level of hemodilution would have been found.

The position of the ODC, corrected for changes in pH and Pco_2, shifted to the right, but not before the hematocrit was 8%. There are no reports concerning the position of the ODC in humans during acute hemodilution, except reports of the ODC during chronic anemia. In two studies in humans, chronically reduced hemoglobin concentration is compensated by improved oxygen unloading, afforded by the shift to the right of the ODC (15,16). In one study in dogs, an acute change in ODC during acute hemodilution occurred but not before the hematocrit decreased below 10% (17), whereas in sedated pigs at every step of hemodilution, the ODC shifted to the right (11,18). In these pig studies, a close relationship was found between the shift in ODC and the decreased mixed venous Po_2 for corrected pH 7.4. Therefore, just as in our case, changes in ODC may play a role in oxygen delivery during acute hemodilution and especially, as stated previously (18,19), when oxygen reserves are minimal.

One might argue that from a single case no meaningful conclusions can be made. However, during the same stages of hemodilution (at the same hematocrit level), the cardiovasular responses to hemodilution of this patient were similar to those in another report on anesthetized humans (1), and this case might therefore be representative for anesthetized humans. Furthermore, the advanced age of the patient could have influenced the critical point of hemodilution. However, in a clinical study there were no differences found between young and elderly patients in hemodynamic compensatory mechanisms during hemodilution (20). Finally, it has been suggested that by calculating Vo_2, rather than measuring Vo_2, and using the same variable (e.g., cardiac output) for calculating Vo_2 and Do_2, the relationship between Do_2 and Vo_2 might be based on mathematic coupling. However, it has been stated that by keeping the range of the independent variables as large as possible (as in our patient), the effects of coupled error are excluded (21).

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Insertion of the Laryngeal Mask Airway in Awake Infants With the Robin Sequence

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Since its development and description, the laryngeal mask airway (LMA) has gained rapid acceptance in Europe and Canada (1,2). The LMA has been slow to gain widespread use in the U.S. anesthesia community owing to the lack of availability and, possibly, the concern for risks incurred with the use of any mask airway, including aspiration and laryngospasm.

Apart from its use in patients with normal airway anatomy, several reports have been published advocating the LMA as an alternative to tracheal intubation in patients ranging from neonates to 9 yr of age with severe micrognathia (3–5). Infants with severe forms of the Robin sequence (also known as Pierre Robin syndrome) may present difficulties in maintaining a mask airway in addition to the challenge of tracheal intubation. On the basis of the reported success of the LMA in anesthetized children with micrognathia, we devised an approach for anesthetizing infants with the Robin sequence with severe micrognathia and airway obstruction. We proposed to insert the LMA in the *awake* infant and then to proceed to induce general anesthesia with the inhalation of halothane. This report is based on the first three patients in whom we utilized this approach.

Case 1

A 4.8-kg, 6-wk-old boy with the Robin sequence, a Dandy-Walker cyst, and recurrent airway obstruction was admitted for revision of a glossopexy originally performed at 4 wk of age. Maintenance of an adequate mask fit and patent airway proved difficult during the administration of the first anesthetic, and direct laryngoscopy had failed to provide visualization of the larynx. Oral tracheal intubation was accomplished using the modified lighted stylet technique described by Krucylak and Schreiner (6).

Subsequent anesthesia was managed as follows: preanesthetic medication consisting of oral atropine (0.02 mg/kg) was administered 30 min before induction of anesthesia. The awake infant's oropharynx was sprayed once with 2% lidocaine solution (~2 mg), and a No. 1 LMA lubricated with 2% viscous lidocaine (~4 mg) was inserted. The child tolerated insertion of the LMA well and neither coughed nor gagged but cried with the same intensity as he did when initially entering the operating room. Breathing was audible through the LMA, and auscultation confirmed bilateral breath sounds. After we induced anesthesia with 1.5% halothane in oxygen and demonstrated the ability to manually control ventilation, the patient was paralyzed with 0.1 mg/kg of intravenous vecuronium. The LMA was removed, and the infant's trachea was intubated on the first attempt using a modified lighted stylet.

This infant returned to the operating room 4 mo later for elective hernia repair. After inhaled induction of anesthesia, fiberoptic bronchoscopy was easily performed using the LMA as a guide, as previously described by Benumof (7) and by Maekawa et al. (8).

Case 2

A 3.4-kg, 5-wk-old girl with the Robin sequence associated with arthrogryposis presented for glossopexy after several weeks of trial management with a nasopharyngeal airway had failed to relieve her obstructive apnea. No preanesthetic medication was given. Topical application of 2% lidocaine solution (~2 mg) to the oropharynx preceded insertion of a No. 1 LMA lubricated with 2% viscous lidocaine (~4 mg) in the awake patient. Although the infant cried, the degree of distress appeared to be comparable to that expressed during the insertion of an orogastric tube in the awake child. A smooth inhaled induction of general anesthesia followed, with a mixture of 50% nitrous oxide and 0.5%–2% halothane in oxygen via the LMA. After demonstrating that we could manually control ventilation, intravenous vecuronium was used to facilitate neuromuscular relaxation. Although only the posterior arytenoids were visible with direct laryngoscopy and cricoid pressure, this proved sufficient for successful tracheal intubation. After extubation of the trachea, the patient required placement of a nasopharyngeal airway and application of continuous positive airway pressure to relieve airway obstruc-

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tion. Three weeks later, the patient returned to the operating room for an elective tracheostomy because of persistent airway obstruction. The induction of anesthesia was identical to that just described. On this occasion, however, tracheal intubation required the use of the lighted stylet.

Case 3

A 2.9-kg, 16-wk-old girl with the Robin sequence associated with Stickler syndrome (progressive arthro-ophthalmopathy) was admitted for tracheostomy to relieve persistent airway obstruction. Stickler syndrome is the most common genetic cause of the Robin sequence and is associated with mandibular hypoplasia, progressive myopia, retinal detachment, and joint stiffness. A glossopexy performed 2 wk previously failed to relieve the infant's recurrent episodes of upper airway obstruction, even with the aid of a nasopharyngeal airway. During the previous anesthetic, the awake infant's trachea had been intubated under direct laryngoscopy. The anesthesiologist performing the intubation had not visualized the larynx but still successfully intubated the trachea using a styletted endotracheal tube.

Because of persistent severe airway obstruction and previous difficulty with tracheal intubation, we altered our approach. Oropharyngeal topical analgesia was accomplished with a single spray of 2% lidocaine solution (~2 mg). A No. 1 LMA lubricated with 2% viscous lidocaine (~4 mg) was inserted in the awake patient, who tolerated this, crying with breath sounds clearly audible through the LMA. We proceeded to induce general anesthesia while maintaining spontaneous ventilation with the inhalation of 1.5% halothane in oxygen. After demonstrating that we could manually control ventilation, the patient was paralyzed with intravenous vecuronium. Direct laryngoscopy again failed to allow visualization of the larynx, but this time an attempt at tracheal intubation was unsuccessful. The LMA was easily reinserted, and controlled ventilation was resumed. After removal of the LMA, the trachea was intubated using a lighted stylet.

Discussion

The Robin sequence represents a spectrum of anatomic anomalies the common features of which include mandibular hypoplasia, glossoptosis, and cleft palate. Four types of airway obstruction have been described in patients with the Robin sequence; in only 50% is the obstruction totally related to posterior positioning of the tongue (9). Therefore glossopexy will fail to relieve airway obstruction in approximately half of all symptomatic patients with the Robin sequence. This may explain why the use of an oral or nasopharyngeal airway alone may not improve an already difficult mask airway. Patients who fail to improve after glossopexy or nasopharyngeal airway placement, or both, usually require tracheostomy.

During inhaled induction of general anesthesia via a mask in infants and children with abnormal airway anatomy, as seen in Robin sequence, upper airway obstruction is usually anticipated, often encountered, and occasionally extremely difficult to manage. We have described three infants with severe airway obstruction unrelieved by placement of a nasopharyngeal airway. Insertion of an LMA while these infants were still awake secured a patent airway before the induction of general anesthesia. Once the infants were anesthetized, the anesthesiologist could calmly proceed with the task of tracheal intubation. Had the procedures been non-airway related, the LMA would have provided an alternative to tracheal intubation. Reinsertion of the LMA between attempts at tracheal intubation provided excellent airway control.

Visualization of the larynx may prove difficult or impossible in patients with the Robin sequence. Some of the approaches that have proved successful when conventional direct laryngoscopy has failed include direct laryngoscopy with an anterior commissure laryngoscope (10,11), fiberoptic bronchoscopy (7,8,12), and intubation with a lighted stylet (6). Over the past 2 yr, we have had consistent success with intubating the trachea of infants and children with severe micrognathia using a lighted stylet. In teaching this last technique to our less experienced colleagues, we insist that they become comfortable with this technique in healthy children >10 yr old before attempting it in healthy younger children and infants. Only in this fashion can one safely achieve successful intubation of the trachea in smaller patients with a complicated airway anatomy. Although older children can usually be safely sedated and intubated using the fiberoptic bronchoscope alone, in infants this may be more difficult. Bronchoscopes as thin as 2.2 mm in diameter are now available, making fiberoptic bronchoscopy through the LMA (7,8) a viable alternative for those less comfortable with the use of a lighted stylet.

It must be emphasized that all of the complications of mask anesthesia, including emesis and aspiration, can occur with the LMA. Although the most caudal tip of the LMA is positioned in the floor of the hypopharynx (Figure 1), this does not provide protection against active regurgitation. In one report, a patient undergoing a cholecystectomy aspirated stomach contents intraoperatively. This was detected only after removal of the LMA (13). In a second report, vomiting resulting in aspiration pneumonitis developed in a 74-yr-old man undergoing a hip arthroplasty using an LMA (14). The authors attributed the vomiting to inadequate depth of anesthesia. Regurgitated material can be more difficult to recognize when using the LMA; once discovered, the LMA and oropharynx should be suctioned and the LMA

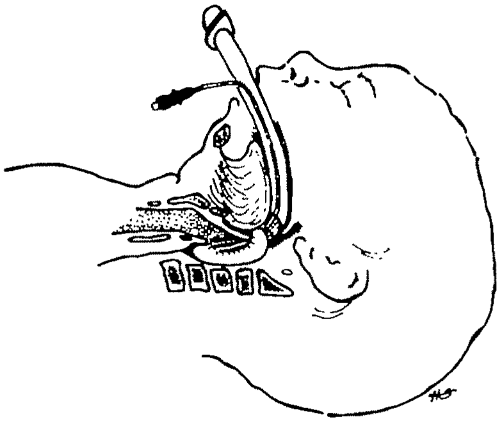

Figure 1. The laryngeal mask airway bypasses the soft tissue obstruction by surrounding the infant's larynx.

removed. The other potential complications of LMA, as seen in mask anesthesia, include laryngospasm, coughing, or breath holding. These complications were not seen in the infants reported here, perhaps because the LMA was inserted while the infants were still awake. Were laryngospasm encountered during the insertion of the LMA, we would recommend the use of succinylcholine and subsequent ventilation through the LMA, striving for a more adequate depth of anesthesia. Malposition of the LMA should be detected if breath sounds are not adequate or if there is a large air leak of the oropharynx.

The three infants cried when the LMA was inserted, but the level of stress appeared comparable to the insertion of an orogastric or nasogastric tube in an awake infant. The infant's reaction did not, therefore, prevent a smooth induction of anesthesia. Although we used both lidocaine solution spray and viscous lidocaine as a lubricant to provide topical anesthesia to the pharynx, it is not clear that both were necessary. To avoid potentially toxic doses of lidocaine in infants, the LMA lubricant might best be lidocaine free, using lidocaine spray alone for topicalization.

One could argue that the use of a shorter acting muscle relaxant than vecuronium might be preferable; however, this might not afford the time occasionally required to intubate using either the lighted stylet or the fiberoptic bronchoscope. Our choice of an intermediate-acting nondepolarizing relaxant reflected our confidence in having secured and confirmed a patent airway before the induction of general anesthesia, our ability to control ventilation after the induction of anesthesia, and our confidence in our ability to easily replace the LMA once it had been removed.

We have demonstrated that in infants with the Robin sequence and severe airway obstruction, the LMA allows a smooth transition from the awake, spontaneously breathing state to the anesthetized state while avoiding episodes of airway obstruction in the interim. After ensuring the ability to provide adequate positive pressure ventilation, neuromuscular blockade can be used if desired. With the patient well ventilated, anesthetized, and paralyzed, optimal conditions exist for successful, atraumatic tracheal intubation.

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Extracorporeal Membrane Oxygenation for Perioperative Support During Congenital Tracheal Stenosis Repair

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Extracorporeal membrane oxygenation (ECMO) is routinely used for cardiopulmonary support in a wide variety of neonatal diseases, such as meconium aspiration syndrome, respiratory distress syndrome, persistent pulmonary hypertension, sepsis syndrome, and severe pneumonia. Extracorporeal membrane oxygenation is also potentially useful as a component of preoperative care for infants with profound respiratory failure and surgical lesions such as congenital diaphragmatic hernia (1). We recently used ECMO intraoperatively to support a baby with congenital tracheal stenosis (CTS) and continued using ECMO during the postoperative period to avoid trauma to the tracheal anastomosis. Extracorporeal membrane oxygenation was continued for 7 days, after which the patient was safely returned to mechanical ventilation. This hybrid approach is similar to that used in patients with unrepaired congenital diaphragmatic hernia (2).

Neonatal CTS, which presents with severe symptoms in the first days of life, has a high mortality (44%–79%), and sudden death is common (3,4). If the lesion is near or includes the carina or involves >50% of the trachea, repair is both difficult and dangerous. A variety of surgical approaches have been used. The surgical repair of choice is primary tracheal resection and anastomosis (5). Most surgeons believe that up to 50% of the length of the infant trachea can be primarily resected (1). Where the lesion involves >50% of the trachea, tracheal reconstruction has been performed using a variety of materials to fill the defect, including costochondral grafts (3,6), pericardium (7), and esophagus (4).

Regardless of the method of repair, providing ventilation and oxygenation during surgical correction of the trachea is one of the anesthesiologist's greatest challenges. If an endotracheal tube can be advanced through the area of stenosis to the carina or into one lung, ventilatory support can be maintained in a traditional fashion. This is often fraught with technical difficulties and a significant risk of hypoxia, hypercarbia, and neurologic sequelae (1). When the airway cannot be dependably secured, management alternatives include the use of cardiopulmonary bypass (CPB) to maintain CO_2 removal and oxygenation (4,5,7) or jet ventilation (8). Traditional CPB requires a median sternotomy with placement of aortic and right atrial catheters. Patients must undergo heparinization so that extracorporeal circuitry can be used without clotting. In addition, standard CPB cannulation further complicates the surgical approach with large catheters in the operative field. Even if the operation goes smoothly, postbypass ventilation may be difficult or unsuccessful. Recently, in a baby with CTS, we elected to use ECMO to provide perioperative ventilatory support. A form of extracorporeal support was chosen because the pinpoint stenosis was at the carina, and a mainstem bronchus could not be safely intubated. Extracorporeal membrane oxygenation provided secure intraoperative gas exchange and assured a stable postoperative period while minimizing barotrauma and mechanical trauma to the anastomosis.

Case Report

A 2.5-kg full-term infant was twin A, delivered by elective cesarean section at 38-wk gestation. She had Apgar scores of 8 at 1 min and 9 at 5 min. Respiratory distress rapidly developed in the delivery room, with gasping respirations, grunting, and cyanosis. The baby was transferred to the neonatal intensive care unit and the trachea was intubated with a 3.5-mm endotracheal tube. Arterial blood gas revealed pH 6.98, P_{CO_2} 108 mm Hg, P_{O_2} 69 mm Hg, 0.35 fraction of inspired oxygen (F_{IO_2}) ventilatory pressures of 22/3 cm H_2O, and intermittent mechanical ventilation of 60 breaths/min. A chest radiograph before intubation showed hypoinflation. After intubation, marked bilateral hyperinflation with hyperlucent lung fields and flattened dia-

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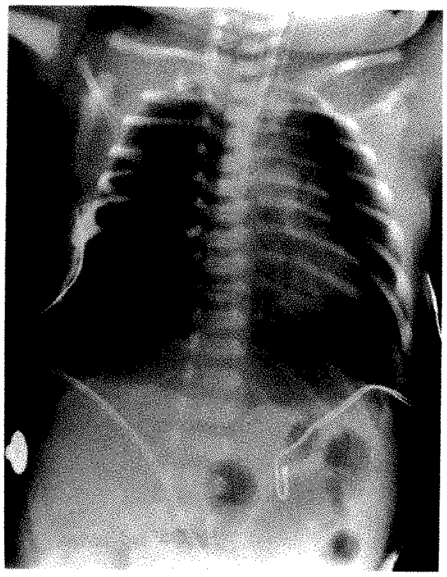

igure 1. Chest radiograph soon after birth, showing the marked yperinflation of the lungs with flattening of the diaphragms. Vhat is also remarkable is the lack of tracheal shadow from the end f the endotracheal tube to the appearance of the mainstem ronchi.

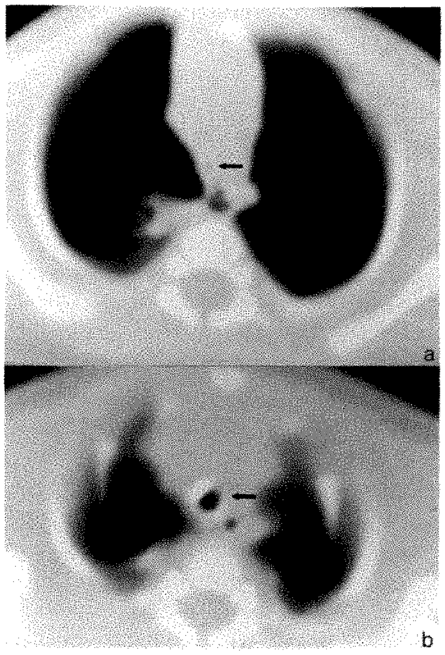

Figure 2. a. Computed tomography scan view showing the narrowed trachea just at the carina (*arrow*). In contrast, just posterior to the trachea is the esophagus with a 5F feeding tube. **b.** Normal trachea just distal to the end of the endotracheal tube (*arrow*). Again, for contrast, just posterior to the trachea is the 5F feeding tube in the esophagus.

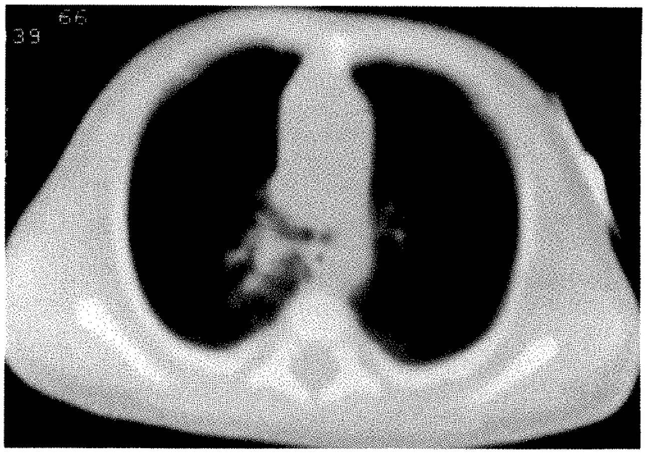

Figure 3. Computed tomography scan view shows the normal caliber mainstem bronchi just distal to the carina.

hragms was evident (Figure 1). Numerous ventilator ianipulations and reintubation with a 4.0-mm endotraheal tube were unsuccessful in resolving the hypercarbia nd hyperinflation.

Bronchoscopy on day 3 of life revealed severe distal acheal stenosis with circumferential narrowing that did ot admit a 3-mm bronchoscope. A high-resolution comuted tomography scan showed a 1.5-cm segment of cirumferential tracheal narrowing approximately 1 mm in iameter, without cartilaginous rings, that extended to the arina but did not appear to involve the mainstem bronchi igure 2). Both mainstem bronchi appeared to be of normal ize just after their origin (Figure 3). An echocardiogram as performed that showed no structural heart disease, nd an ultrasound examination of the brain revealed no emorrhage or structural abnormalities. In the 24 h before urgery, there was a need for increased FIO$_2$ to 0.4. The hest radiograph remained clear, but the lungs were hyperflated.

Because of the location of the stenotic lesion and the aliber of the trachea (1–2 mm), intraoperative extracorpoeal circulation was chosen to facilitate operative repair. enoarterial (VA) ECMO was chosen because it allowed e use of extracorporeal support without a median sternomy and bulky cannulas in a small (2.5 kg) infant. Extrarporeal membrane oxygenation also allowed the use of orter activated clotting times (ACTs) than CPB and alwed the operative repair to be performed from a supraavicular approach without thoracotomy or sternotomy. In ddition, ECMO provided the option of postoperative pport.

The infant was positioned with cervical hyperextension, lowing easy visualization of the trachea. Anesthesia was rovided by 20 μg/kg of fentanyl and muscle paralysis with 0.3 mg of pancuronium bromide. Ventilation was maintained with a Mapelson D circuit and FIO$_2$ was titrated to maintain 95% arterial saturation. End-tidal CO$_2$ monitoring (Raman spectroscopy, aspiration from a distal endotracheal tube) and pulse oximetry saturation were used to guide hand ventilation and FIO$_2$. Careful dissection using meticulous electrocoagulation allowed mobilization of the trachea and identification of the area of tight stenosis. The right common carotid artery and right internal jugular vein were isolated and prepared for cannulation with the ECMO catheters, which were eventually inserted posterior to the sternocleidomastoid muscle. The catheters exited from the primary surgical incision, because making separate stab wounds would increase the likelihood of postoperative bleeding on ECMO. The catheters were compartmentalized from the site of the surgical repair by the sternocleidomastoid muscle. The distal trachea was widely mobilized to visualize the mainstem bronchi. The baby underwent heparinization with 100 U/kg of sodium heparin. The ECMO catheters (BioMedicus, Eden Prairie, Minn.), an 8F arterial and 10F venous, were placed and the position verified by chest radiograph. Venoarterial ECMO support was initiated and stabilized over 15 min. Ventilation through the endotracheal tube was discontinued. The endotracheal tube remained in place, well above the area of repair.

Anesthesia was supplemented with 20 μg/kg of fentanyl, 0.5 mg of midazolam, and an additional 0.5 mg of pancuronium bromide. A heparin infusion was adjusted to maintain ACTs of 180–200 s using the Hemochron (International Technidyne Corporation, Edison, N.J.) system. The platelet count was 160,000/mm^3 before beginning CPB. Aggressive transfusion was used to maintain the platelet count between 150,000 and 200,000/mm^3 to minimize bleeding. Extracorporeal membrane oxygenation flows were maintained at 80 mL·kg^{-1}·min^{-1}. This flow maintained a stable venous saturation of 70% and normalized arterial blood gases. In neonatal ECMO support for respiratory failure, 80–120 mL·kg^{-1}·min^{-1} generally provides excellent gas exchange support without native pulmonary function (9). The stenotic area of trachea was resected, and primary anastomosis was successfully completed. During the repair, the baby remained hemodynamically stable without CO_2 retention, hypoxemia, or acidosis.

The baby was returned to the pediatric intensive care unit on ECMO with continuous positive airway pressure of 5 cm H_2O without ventilation. Extracorporeal membrane oxygenation was continued for 7 days. The baby underwent elective flexible bronchoscopy twice during ECMO to document the patency and stability of the anastomotic site and to remove tenacious secretions that transiently occluded the trachea, resulting in bilateral atelectasis. Blind, deep tracheal suctioning was avoided to minimize trauma to the anastomosis. The endotracheal suction catheters were passed only to the end of the endotracheal tube during routine suctioning. The postoperative course was complicated by large, bilateral pleural effusions that required pleurocentesis just before discontinuing ECMO. Extracorporeal membrane oxygenation was discontinued on the seventh postoperative day, when bronchoscopy revealed a well-healed, open tracheal anastomosis. The operative incision was without bleeding until the last 12–24 h of ECMO. There were no signs of wound infection. Prophylactic antibiotic coverage with oxacillin and gentamicin was maintained during ECMO. There were no episodes of desaturation or hemodynamic instability during ECMO. Eight months after repair, the infant remains dependent on ventilatory support because of tracheomalacia.

Discussion

Neonatal CTS is a life-threatening disease, particularly if it involves a long segment. Before the 1980s, severe tracheal stenosis was nearly always fatal (8). In most recent reports, mortality remains high despite the many surgical advances in therapy (3,4). If the lesion is near or involves the carina, the repair is technically much more difficult. In infants with early symptomatology, the risk of sudden death from tracheal obstruction is significant (3,4), and many survivors have profound neurologic injury as a result of hypoxic insults before or during repair (1,3,8).

Because of the distal location of this stenotic lesion and the degree of carinal involvement, we believed that ventilation through the airway would be extremely difficult, potentially impossible, and would technically complicate the surgical repair. Extracorporeal support greatly facilitated the repair and provided postoperative support. A median sternotomy with intrathoracic catheters for standard CPB would have exposed this small infant (2.5 kg) to added risk and contributed to a crowded operative field. Because extracorporeal support could be easily accomplished through the cervical incision using VA ECMO, this approach to intraoperative support was attractive, albeit unique. Other potential benefits of ECMO included (a) lower heparin requirement for heparinization than CPB, with decreased risk of bleeding; and (b) the option of providing extracorporeal support postoperatively allowed potential protection of the anastomosis from the stresses of mechanical ventilation and suctioning during the early postoperative period.

The major complications of ECMO are neurologic injury, bleeding, embolism, and sepsis. Neurologic injury is related to cannulation and ligation of the common carotid artery and internal jugular vein and bleeding and embolism during bypass. Acute VA ECMO with vessel ligation is generally well tolerated by critically ill infants in severe respiratory failure. Follow-up studies in infants supported with ECMO have shown that developmental outcome is similar to that seen in infants with serious respiratory failure treated conventionally (10). Two extensive neuroimaging follow-up series of neonates who required support with ECMO have failed to demonstrate any difference in the numbers of right-sided (ligated) versus left-sided (unligated) intracranial lesions (11,12). Those infants may, however, have suffered pre-ECMO neurologic injury due to an underlying disease process that required ECMO. One would expect VA ECMO to be better tolerated in an infant without antecedent hypotension or hypoxia. There are alternative sites and strategies for ECMO that include venovenous support or alternative sites for arterial cannulation. It is difficult to provide good oxygenation with venovenous ECMO without some pulmonary contribution, which has made it a less than satisfactory form of support for the operative procedure. In an infant of this size (2.5 kg), other arterial sites are too small. A recent report (13) describes the use of a side-sewn carotid patch that does not require carotid ligation and was described as easily repaired. This could be considered an option.

Risks of prolonged ECMO support include hemorrhage from continued use of heparin, risks of thrombi or emboli from long-term arterial infusion, and infection from continued maintenance of catheters near the operative site. The risk of hemorrhage in this case was greatest at the time and site of surgical repair. The ACTs were maintained in the 180–200-s range, and aggressive postoperative transfusion of platelets achieved an elevated platelet count of 150,000/mm^3 to minimize this risk. The thrombotic or embolic risk is real, but with meticulous care, many hours of prolonged bypass can be performed without incident (14). To prevent or minimize the risk of infection, the perfusion catheters were separated from the operative incision by compartmentalization with the sternocleidomastoid muscle. Prophylactic antibiotics (oxacillin and gentamicin) were also administered.

Intraoperative anesthetic care consisted of routine monitoring for neonatal surgery, including an arterial cannula (15). In addition, ECMO flows and arterial blood gases, as well as ACTs and heparin infusion rates, required meticulous attention. Fentanyl analgesia was titrated to hemodynamic status. Although ECMO patients show rapid development of fentanyl tolerance, this is generally not evident at the initiation of ECMO (16). Standard doses of fentanyl and muscle relaxants can be used, but as bypass is initiated, there is a decrease in plasma opiate levels, and one must be prepared to supplement analgesia as indicated (17). Hemodynamic instability, hypotension or hypertension, and myocardial "stun" manifested as depression of pulsatility can all occur after the initiation of ECMO. Thus, the hemodynamic status requires careful observation and adjustment of ECMO flows. Full, stable ECMO support should be achieved before surgery proceeds.

Initiation of ECMO support and surgical repair were successfully completed with a primary anastomosis of the carinal cuff to the prestenotic trachea. The child was returned, on ECMO, to the pediatric intensive care unit. During the next 7 days, the infant was easily supported on low continuous positive airway pressure (6–7 cm H_2O). Positive pressure ventilation was completely avoided for the first 48 h and then instituted at 5 breaths/min with a pressure limit of 15 cm H_2O to minimize barotrauma to the tracheal anastomosis. Elective bronchoscopy to monitor the site of anastomosis and clear secretions was easily accomplished using a 3-mm flexible bronchoscope. Extracorporeal membrane oxygenation was discontinued on day 7, when the anastomosis was noted to be open and healing well. The lungs were well expanded after thoracentesis. The decision to discontinue support at day 7 was based on two factors. First, a healthy, healing anastomotic site was seen on bronchoscopy; and second, the first evidence of bleeding was observed (1–2 $mL \cdot kg^{-1} \cdot h^{-1}$) from the suprasternal incision. If some bleeding had not begun, we might have considered extracorporeal support for a slightly longer period to assure maximal anastomotic healing.

In this child, ECMO was chosen instead of traditional CPB because median sternotomy and intracardiac cannulation could be avoided, less heparinization was possible, and prolonged (several days) postoperative support could be provided. The prolonged postoperative support was the most significant issue. It was clear that this baby would require mechanical ventilatory support postoperatively. We believed that the benefits of low continuous positive airway pressure without the need for intermittent positive pressure ventilation would enhance anastomotic healing, owing to less stress and tension on the suture line.

In conclusion, intraoperative ECMO provided a safe, controlled method of intraoperative respiratory support while optimizing surgical conditions. In this child with paracarinal CTS, ECMO also provided postoperative support to enhance tracheal healing and pulmonary recovery.

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Management of a Difficult Airway in a Patient With Hurler-Scheie Syndrome During Cardiac Surgery

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The mucopolysaccharidoses (MPS) are a heterogeneous group of clinically progressive inherited diseases characterized by excessive storage of mucopolysaccharides leading to organ dysfunction and anatomic abnormalities. Even though the MPS are rare disorders, their disabling and progressive nature involves frequent surgical intervention, which is accompanied by an increased risk of perioperative complications, many related to the anesthetic. The major features of these syndromes that have anesthetic implications include progressive airway, craniofacial, and skeletal abnormalities and developmental delay (1–5). We present the use of extracorporeal circulation as an alternative method for managing a known difficult airway in a patient with MPS scheduled for open heart surgery.

Case Report

A 20-yr-old man with Hurler-Scheie syndrome (MPS type V) was scheduled for aortic and mitral valve replacement because of stenosis of both valves. Mucopolysaccharide deposition had required balloon valvotomy of the mitral valve and of both valves 5 and 1 yr, respectively, before surgery. Progressive exercise intolerance, chest discomfort, and dyspnea prompted repeat cardiac catheterization, which demonstrated an aortic valve gradient of 100 mm Hg with a pulmonary artery pressure of 48/36 mm Hg and wedge pressure of 32 mm Hg. The patient reported progressive airway obstruction during sleep over the 4 yr before surgery. Nasal continuous positive airway pressure (10 cm H_2O) and sleeping in the sitting position improved airway patency. The patient had undergone two previous surgical procedures for which he received a general endotracheal anesthetic: an inguinal herniorrhaphy in infancy and an Achilles tendon release at age 6 yr. A carpal tunnel procedure at 9 yr was abandoned because of an inability to intubate the trachea following induction of anesthesia. A subsequent corneal transplant, as well as the balloon valvotomies, was performed with sedation with the patient in the semirecumbent position. Preoperative physical examination revealed an alert, cooperative man with normal mental status who weighed 37 kg and whose height was 127 cm. Arterial blood pressure was 105/70 mm Hg, heart rate was 60 bpm, respiratory rate was 30 breaths/min, and peripheral arterial oxygen saturation measured by a pulse oximeter sensor while breathing room air was 96%. Evaluation of his airway demonstrated a mental to hyoid distance of 1.5 finger breadths, macroglossia, restricted motion of his tempromandibular joints and neck, redundant pharyngeal tissue, and tonsilar hypertrophy.

The patient was orally premedicated with atropine (0.02 mg/kg). After placement of peripheral venous and radial arterial catheters, electrocardiogram leads, and a pulse oximeter sensor, a topical laryngeal block was performed using 4% lidocaine. Two unsuccessful attempts, one via the oral and the other via the nasal route, were made to place an endotracheal tube using a fiberoptic bronchoscope with the patient in the sitting position. Anesthesia was then electively induced with intravenous ketamine (2 mg/kg) and the patient was placed supine. With the patient breathing 100% oxygen via a face mask delivering 10 cm of positive pressure, the right groin was infiltrated with local anesthetic and arterial and venous bypass cannulas were placed in the patient's femoral artery and vein. Cardiopulmonary bypass was instituted using a pump priming volume containing pancuronium (0.2 mg/kg), fentanyl (75 μg/kg), and scopolamine (0.01 mg/kg), after which the heart was exposed via a median sternotomy. Hypothermic circulatory arrest was begun once the patient was cooled to a rectal temperature of 20°C, during which time both valves were excised and replaced. A number of experienced anesthesiologists made several attempts using all available modalities (variety of laryngoscope blades, anterior commissure laryngoscope, lightwand, fiberoptic bronchoscope, blind nasal) to intubate the trachea without success by the time of rewarming after completion of the surgery. A decision had been made for the surgeon to introduce a 75-cm, 0.045-mm wire into a small incision in the thoracic trachea and pass it cephalad to exit the nose. After failing to pass a 6.0-mm cuffed tube, a 5.0-mm uncut cuffed endotracheal tube was guided over the wire and, while keeping the wire taut, the tube was

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advanced into the trachea. Visual inspection of lung expansion enabled identification of the carina. The tube was then placed 2 cm proximal to the carina and the cuff inflated. The patient was successfully weaned from bypass and transferred to the intensive care unit where the postoperative chest radiograph showed the nasotracheal tube to be in proper position. The endotracheal tube remained in place, with no attempt made to extubate the trachea for the next 3 days, at which time the patient died for reasons unrelated to his airway.

Discussion

This case illustrates an alternative method for managing a difficult airway in a patient having cardiac surgery with extracorporeal circulation. After preoperative identification of a problematic airway, a plan is devised for the patient to maintain spontaneous ventilation until institution of bypass. Once the patient is on bypass, oxygenation and ventilation are assured and attempts can be made to secure the airway with an endotracheal tube. This approach when properly executed eliminates the potential for inadequate oxygenation and/or ventilation and hemodynamic compromise when placing an endotracheal tube in a patient with a difficult airway. Consideration must be given to the potential risks associated with this technique, including loss of the airway before institution of bypass if sedative medications are used, airway manipulation in an anticoagulated patient, and inability to place an endotracheal tube after institution of bypass. The history of inability to intubate this patient's trachea, the inability of the patient to lie flat without acute dypsnea and upper airway obstruction, and the undesirability of tracheostomy called for careful and innovative management. An anesthetic plan was constructed recognizing that this patient was to undergo surgery requiring cardiopulmonary bypass. A minimal number of attempts to intubate the topicalized airway using conventional modalities were planned while the patient was awake, thus minimizing both trauma to the airway and alterations in hemodynamics. Recognizing that tracheal intubation via this route was not likely to be successful, consideration was given to attempting a technique that had previously been used in a patient with MPS: placement of the tube over a wire inserted into the larynx via the cricothyroid membrane which was passed retrograde (5). Distortion of the anatomy did not allow distinct identification of the cricothyroid membrane in this patient. The intent was to administer medication to allow the patient to lie flat cooperatively while breathing spontaneously during placement of the bypass cannulas in the groin. Ketamine, in a dose of 2 mg/kg, was chosen as it had met similar goals when used in the same dose in this patient during cardiac catheterizations. Institution of cardiopulmonary bypass would then enable additional attempts to intubate the trachea with no stress to the cardiovascular system while oxygenation and ventilation were guaranteed. Recognizing that, despite ideal conditions, the anatomic abnormalities of the airway might preclude both oral and nasal intubation, an attempt would be made to place an endotracheal tube over a wire inserted into the thoracic trachea and passed retrograde. Tracheostomy, although not desirable because of the proximity of the stoma to the fresh median sternotomy, would secure the airway before weaning from bypass if all other routes failed.

Accumulation of mucopolysaccharides in the soft tissue of the oropharynx, the epiglottis, aryepiglottic folds, and tracheal wall, coupled with the presence of a short neck, predispose these patients to anatomic abnormalities of the airway, tracheal rigidity, and a reduced cross-sectional area. This explains the high incidence of perioperative airway problems, some fatal, reported in these patients. King et al. (3) reported one or more airway problems (difficulty visualizing the cords, inability to pass an age-appropriate tube, and airway obstruction) in all but one of eight pediatric patients between 1 and 16 yr of age with MPS receiving an anesthetic. Baines et al. (2) retrospectively reviewed the anesthetic management of 16 patients with MPS undergoing 50 surgical procedures under general anesthesia. Eight patients had airway difficulty during one or more of their procedures. The trachea of one child could not be intubated. One patient's trachea was successfully intubated only during a respiratory arrest that followed a failed elective intubation, and one patient had an elective tracheostomy under local anesthesia. Kempthorne and Brown (5) examined the airway problems encountered in nine children anesthetized for 20 surgical procedures. In addition to confirming the high incidence of airway problems, 65% in this series, their review suggested that airway problems increase with increasing patient age, a finding that is consistent with the progressive nature of these diseases.

Cardiac involvement in patients with Hurler-Scheie syndrome is limited to the coronary arteries and valves and most commonly presents with signs of valvular insufficiency or stenosis. The pattern of valve involvement is the same as that which follows rheumatic fever. The mitral valve is most frequently affected, followed by the aortic and tricuspid with nearly equal frequency. Although a case could be made for avoiding the use of ketamine in patients with aortic stenosis, it was chosen to induce anesthesia in this patient, as it had been used during the recent cardiac catheterization with no adverse hemodynamic effects.

Faced with a patient with a known difficult airway scheduled for surgery requiring cardiopulmonary bypass, consideration should be given to establishing bypass and then securing the airway.

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Perioperative Management of Neonatal Ectopia Cordis: Report of Three Cases

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Ectopia cordis or heterotopic heart (1) is a rare congenital cardiac anomaly (<0.1% of all congenital heart defects) that has often defied successful surgical repair because of the magnitude of the chest deformity and its associated anomalies, particularly intracardiac defects and omphaloceles (1,2). An increased awareness of ectopia cordis is now indicated, as the early ultrasound diagnosis of the defect can often be made in utero (2). Although the surgical treatment of ectopia cordis continues to be improved and refined (2), the surgical outcome remains dismal, and survivors are rare. Continued advances may, however, soon improve final outcomes for neonates with ectopic hearts. Three cases of ectopia cordis managed at our institution over the past 8 yr are reported. A synopsis of each infant's immediate preanesthetic cardiopulmonary status and any major therapeutic interventions carried out before initial surgery is presented in Table 1. A current classification system for ectopia cordis is also presented (Table 2), associated congenital anomalies are reported (Table 3), and techniques of perioperative management are reviewed (1,2).

Case Reports

Case 1

A 2495-g female neonate delivered vaginally at 38-wk gestation had Apgar scores of 2 at 1 min and 2 at 5 min. An extrathoracic heart with intact anterior abdominal wall had been recognized and was covered with saline-soaked sterile dressings for transfer of the infant to our institution shortly after birth. Direct echocardiography suggested a double-outlet right ventricle with large ventricular septal defect. Within 4 h of birth, the infant was anesthetized with intravenous fentanyl and pancuronium for surgical coverage of the extrathoracic heart. Surgical attempts to reposition the ectopic heart within the thorax were carried out unsuccessfully for the next 4 h. Orthotopic cardiac repositioning produced cardiac tamponade with bradycardia and hypotension, so a synthetic silo was used to cover the exposed heart without producing cardiac tamponade. During transport to the neonatal intensive care unit, the infant developed sudden bradycardia with hypotension that was refractory to cardiopulmonary resuscitation. A transvenous pacemaker did not restore sinus rhythm, and the infant died 8 h after birth. Chromosomal karyotyping was not performed.

Case 2

A 3900-g female neonate with Apgar scores of 5 at 1 min and 7 at 5 min was delivered at 40-wk gestation by emergency cesarean section because of persistent fetal bradycardia in the breech presentation. An anterior thoracoabdominal defect with extrathoracic heart and omphalocele was recognized at birth (Figure 1). At age 16 h, the infant was anesthetized with fentanyl and pancuronium for surgical coverage of thoracoabdominal defects. Each attempt at orthotopic cardiac repositioning caused asystolic cardiac arrest. Sinus rhythm and blood pressure were restored by internal cardiac massage and intravenous therapy with atropine, calcium chloride, sodium bicarbonate, and epinephrine. As the heart and omphalocele could not be reduced and covered primarily, a Silastic silo was tacked to the skin edges to cover the external heart and omphalocele. Synthetic coverage of the defects also triggered cardiac arrest that responded to repeated resuscitative measures as described. The silo was removed, and extensive skin flaps were undermined, raised circumferentially about the defects, and loosely reapproximated without complete closure of the thorax and abdomen. Thirteen hours postoperatively, the patient developed bradycardia with hypotension unresponsive to cardiac massage and resuscitative drugs. The infant died 27 h after birth. Chromosomal karyotype was 46 XX.

Case 3

A 29-yr-old primigravida was referred to our institution at 34 wk of pregnancy after sonographic diagnosis of extrathoracic heart and associated omphalocele. On the day after admission, a 1940-g male neonate with Apgar scores of 2 at 1 min and 4 at 5 min was delivered by primary cesarean

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Table 1. Immediate Preanesthetic Status and Therapeutic Interventions in Three Infants With Ectopia Cordis

Status	Case 1	Case 2	Case 3
Ectopia type	Thoracic	Thoracoabdominal	Abdominal
Temperature (°C)	36.5	37.0	36.8
Heart rate (bpm)	168	142	156
Arterial blood pressure (mm Hg)	60/30	58/30	75/40
$S_{TC}O_2$ (%)	NA	92	NA
PaO_2 (mm Hg)	55	47	32
$PaCO_2$ (mm Hg)	23	42	51
pHa	7.36	7.35	7.22
Base excess	−13.8	−23	−20
Endotracheal tube OD (mm)	3.0	3.5	3.0
Ventilator rate (breaths/min)	24	60	120
Ventilator pressures (cm H_2O)	20/0	25/4	30/4
Vasopressors	None	None	None
Intravenous fluids	a	a	a

$S_{TC}O_2$, transcutaneous O_2 saturation; PaO_2, arterial O_2 tension; $PaCO_2$, arterial CO_2 tension; OD, outside diameter; NA, not available.
[a] Fluids for all = $D_{10}W$ with 3 mEq NaCl + 2 mEq KCl per 100 mL infused at 8 $mL \cdot kg^{-1} \cdot h^{-1}$.

Table 2. Classification of Ectopia Cordis[a]

Type	No. of cases reported to date	Frequency (%)	Sites of associated anomalies
Cervical (heart covered with skin and precervical fascia)	18	8.2	Sternal cleft Craniofacial Intracardiac
Thoracic (heart exposed or partially covered with skin and presternal fascia)	81	36.8	Chest wall (cleft or bifid sternum) Intracardiac Abdominal wall
Thoracoabdominal (pentalogy of Cantrell)	80	36.3	Chest wall (bifid or absent sternum) Intracardiac Diaphragm Abdominal wall
Abdominal	25	11.4	Intracardiac Diaphragm Abdominal wall
Unclassified	16	7.3	NA
Total	220	100	70+% have major associated anomalies

NA, not applicable.
[a] Adapted with permission from Leca et al. (1).

section under general endotracheal anesthesia. A large ventral wall defect containing the heart, the liver, and small bowel loops was recognized. Echocardiographic evaluation demonstrated an intact sternum; a large omphalocele containing the heart, liver, spleen, and small bowel loops; a double-outlet right ventricle; a large ventricular septal defect; valvular pulmonic stenosis; a patent foramen ovale; total anomalous pulmonary venous return; and an absent pericardium. In addition, the heart was noted to be prolapsed through a large midline defect in the diaphragm. Chromosomal karyotype was 46 XX. High-frequency ventilation with 100% inspired oxygen therapy was instituted for progressive respiratory failure with chronic hypoxemia. On the fifth day of life, the infant developed asystolic cardiac arrest and was not resuscitated.

Discussion

With the increasing use of real-time sonography in obstetrics, the diagnosis of ectopia cordis will be made more frequently in the prenatal period (case 3) (2–5). The prenatal diagnosis of ectopia cordis should stimulate a vigorous sonographic search for other associated anomalies, particularly omphaloceles and craniofacial defects such as microcephaly and hydrocephalus (3–5).

The etiology of ectopia cordis is unknown. A weak association with trisomy 18 (one case) has been suggested, and chromosomal karyotyping is now recommended in all cases to improve genetic coun-

Table 3. Specific Anomalies Associated With Ectopia Cordis in Order of Frequency of Occurrence[a]

Sites of anomalies			
Craniofacial	Chest wall	Intracardiac	Abdominal wall
Microcephaly	Cleft sternum	Septal defects	Omphalocele
Hydrocephalus	Bifid sternum	Outflow tract obstructions	Diastasis recti
Cleft palate	Absent sternum	Cardiac diverticuli	Gastroschisis
Cleft lip		Double-outlet right ventricle	
Anencephaly		Anomalies of caval and pulmonary venous return	
Neural tube defect		Transposition of the great arteries	
		Aortic coarctation	
		Truncus arteriosus	

[a]Data from Leca et al. (1) and Harrison et al. (2).

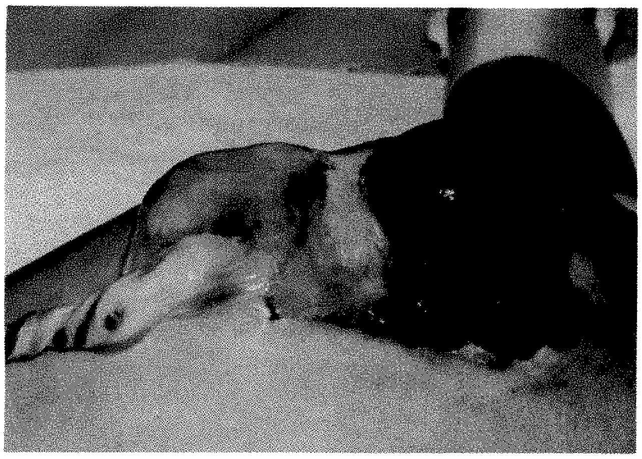

Figure 1. Twelve-hour-old neonate with complete thoracic ectopia cordis and bifid sternum with the entire heart exposed (case 2). Note prominent right and left auricular appendages or diverticuli and associated omphalocele with attached umbilical cord. The right arm is extended for radial artery cannulation (top of photograph).

seling (3,5). Omphalocele and ectopia cordis may both result from the failure of timely fusion of the cephalic anterior body folds and are commonly associated anomalies (6). Some anterior fusion defects and some forms of ectopia cordis may also be caused by the amniotic band syndrome (6).

Early plans may now be made for cesarean delivery of the fetus with ectopia cordis amenable to surgical palliation or repair (2). Vaginal delivery could cause prolonged cardiac compression, damage herniated viscera, or rupture atrial diverticuli or omphalocele sacs (2). After atraumatic abdominal delivery, the neonate with ectopia cordis, omphalocele, and correctable intracardiac anomalies may be considered for staged postnatal repairs (1,2,7). If, however, prenatal echocardiography shows uncorrectable intracardiac lesions, consideration should be given to elective termination of pregnancy in the first or early second trimester (1,3–5,7).

Immediate treatment of an infant with ectopia cordis should begin at birth and consists of covering the lesion with saline-soaked gauze pads and gently wrapping the thorax and trunk circumferentially to prevent heat loss and desiccation of the ectopic heart and omphalocele, if present (2,4). No pressure should be applied over the extrathoracic heart as any compression might reduce venous return to the heart, reduce cardiac filling, and decrease cardiac output. Compression of the omphalocele sac should also be avoided as it may force herniated viscera into a limited abdominal cavity, elevating the hemidiaphragms and restricting alveolar ventilation (8).

After emergency management, more complete preoperative evaluation can be undertaken, such as computerized axial tomography to evaluate thoracic volumes and capacities (6) and echocardiography to confirm the presence or absence of commonly associated intracardiac defects (6) (Table 2). In hemodynamically stable neonates, the extrathoracic heart should then be quickly covered with skin flaps or a synthetic silo or chimney to prevent further fluid loss and cardiac desiccation and to provide soft tissue or synthetic protection of the exposed heart and any associated atrial diverticuli easily ruptured by minor trauma (4).

In a 1982 report, Harrison et al. (2) immediately applied an adherent plastic drape over an intact omphalocele sac in a newborn with thoracoabdominal ectopia cordis. Progressive ligation of the plastic-reinforced sac allowed the omphalocele contents to be gradually reduced by gravity and progressive replacement (2). After temporary coverage of the defect, diagnostic work-up can continue with cardiac catheterization and angiography. Following complete cardiac evaluation after temporary coverage of thoracoabdominal defects, Harrison et al. (2) recommended correction of intracardiac lesions before extensive reconstruction of the chest and abdominal wall, pericardium, and diaphragm. Such extensive operations appear to be poorly tolerated in infants with giant omphaloceles and congenital heart defects (2).

Intraoperative anesthetic management (cases 1 and 2) requires neuromuscular paralysis, controlled hyperventilation for respiratory acidosis, avoidance of high mean airway pressures that could impede biventricular outflows, high inspired O_2 concentrations to improve blood and tissue oxygenation in cases characterized by low cardiac output syndrome and tissue ischemia, and avoidance of nitrous oxide which could distend bowel trapped in omphaloceles. In addition, the hemodynamic instability produced by heart and great vessel dissection contraindicates inhaled anesthetic agents that could promote further myocardial depression in neonates already compromised by extensive fluid losses from herniated viscera, and by respiratory and metabolic acidosis from alveolar hypoventilation and low cardiac output syndrome, respectively. Opiates and ketamine are often the only anesthetics that can be safely used.

Extensive intraoperative monitoring is required, including direct blood pressure measurement by intraarterial cannulas and bladder catheterization for accurate urine outputs. Direct blood pressure measurement by right radial artery cannula is recommended as other arterial sites provide inaccurate blood gas measurements during reestablishment of transitional circulation, which often complicates the postoperative course in neonates with patent ductus awaiting later intracardiac repairs. A pulse oximeter probe on the right hand or right ear also provides continuous preductal monitoring of peripheral perfusion and tissue oxygenation.

Although useful in directing massive volume replacement during thoracic dissection, central venous cannulation for right atrial pressure monitoring may be difficult or impossible because of atrial diverticuli and abnormal systemic and pulmonary venous drainage. Left atrial pressure monitoring may prove just as difficult or impossible for the same reasons. Needle atriotomy with a small-bore catheter through the needle will provide accurate intraoperative central venous pressure monitoring. Transthoracic right atrial cannulation may be helpful after staged repairs of ectopia cordis. Postoperatively, significant artifactual alterations will occur in right atrial waveforms during positive pressure ventilation in infants with either artificially covered or primarily repaired ectopic hearts because of cardiac compression and absence or instability of the anterior chest wall and diaphragm. To limit artifact, right atrial pressures should be measured only at end-exhalation without application of raised airway pressures. In the absence of supravalvular and branch pulmonary artery stenosis, a transthoracic pulmonary artery catheter may be inserted under direct vision through a right ventricular outflow tract ventriculotomy needle. The pulmonary artery catheter may permit better hemodynamic monitoring during low cardiac output states, persistent pulmonary hypertension, or prolonged pulmonary hypoplasia and allow for thermodilution cardiac output determinations postoperatively. As with right atrial pressures, pulmonary arterial pressures should be measured only at end-exhalation without application of raised airway pressures that could induce artifactual fluctuations in waveforms.

Endotracheal tubes should remain in place until infants are conscious and vigorous with normal arterial blood gases, tidal volumes, and ventilatory mechanics, usually several days to weeks postoperatively (9). Tight skin or synthetic-silo closures of the thorax and abdominal wall can significantly restrict spontaneous ventilation and prolong the need for postoperative controlled ventilation (9). Tissue expanders create larger skin and subcutaneous tissue flaps for subsequent defect closures with less restriction of ventilation and may permit earlier tracheal extubation postoperatively (9).

Cardiovascular failure, particularly from undiagnosed or uncorrected associated cardiac anomalies and rupture of cardiac diverticuli (1,7), and cardiorespiratory failure are frequent causes of death in the immediate postoperative period (Figure 1). Although never used in the management of ectopia cordis, extracorporeal membrane oxygenation may provide a better therapeutic bridge between defect coverage and later intracardiac or reconstructive surgery than inotropes alone. Further operations for wound dehiscence, secondary wound closures, or relaxing incisions may be necessary in the first few weeks postoperatively (1,7).

Orthotopic heart transplantation has not been suggested as a viable alternative for the initial surgical management of ectopia cordis probably because associated chest and abdominal wall defects often need several staged repairs in an immunocompetent patient. After successful chest and abdominal wall closures, however, the infant with ectopia cordis and uncorrectable intracardiac defects may become a candidate for orthotopic heart transplantation, provided the recipient's great vessel anatomy and pulmonary venous drainage are amenable to standard donor-recipient vascular anastomoses.

In conclusion, the frequency of accurate in utero diagnosis of ectopia cordis is increasing. The extent of chest and abdominal wall deformities in ectopia cordis has often defied previous attempts at surgical repair. Extensive thoracic dissection to free the great vessels and to create more mediastinal space for a deformed heart that was later compressed by tight silo (case 1) or skin (case 2) closures led to the early postoperative death of patients 1 and 2, respectively, resulting from progressive intravascular volume losses, limitation of venous return, reduction of cardiac output, and pump failure. Prenatal sonographic diagnosis, abdominal delivery, neonatal resuscitation, and temporary and nonrestricting synthetic or skin coverage of thoracoabdominal defects may be followed by intracardiac repair and chest wall reconstruction in neonates with ectopia cordis. These efforts, combined with advances in surgical techniques, infant heart transplantation, and the newer cardiorespiratory support technologies, like extracorporeal membrane oxygenation, may soon improve the likelihood of quality survival in ectopia cordis.

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Intraoperative Hypoxemia Complicating Laparoscopic Cholecystectomy in a Patient With Sickle Hemoglobinopathy

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Laparoscopic cholecystectomy has recently become a popular alternative to traditional laparotomy and cholecystectomy in the management of patients with gallbladder disease (1). This new surgical technique retains the benefit of completely removing the gallbladder with the advantages of shorter hospital stay, more rapid return to normal activities, less pain associated with the small, limited incisions, and less postoperative ileus compared with the open laparotomy technique (2–4).

The sickle hemoglobinopathies are inherited hematologic disorders characterized by the presence of hemoglobin S (Hb S) and in vivo sickling of erythrocytes. Chronic hemolytic anemia associated with sickle hemoglobinopathy predisposes the individual to cholelithiasis. The reported presence of cholelithiasis in patients with sickle cell hemoglobinopathies ranges from 4% when diagnosed by routine abdominal radiography and oral cholecystography (5) to 55% when ultrasonography is used (6). Regarding the indications for cholecystectomy, surgical opinion remains divided between those advocating the procedure only for symptomatic patients because of increased operative risks (7) and those recommending elective cholecystectomy for patients with silent gallstones to avoid future complications and diagnostic difficulties differentiating acute cholecystitis from hepatobiliary sickle cell crisis (8).

Early contraindications to the laparoscopic cholecystectomy technique included the presence of large intrabiliary stones, common bile duct stones, evidence of acute inflammation, or pregnancy (9). Morbid obesity and the possibility of adhesions associated with previous intraabdominal surgery were considered relative contraindications. The indications for the laparoscopic technique have become more liberal recently after case reports confirmed its efficacy and safety in patients with acute cholecystitis (10) and during pregnancy (11). A recent report described the safe use of laparoscopic cholecystectomy in nine young patients with sickle hemoglobinopathy (12). However, the presence of preexisting lung disease has not been considered a relative contraindication to laparoscopic cholecystectomy. We present the first report of the necessity for conversion to an open cholecystectomy because of profound and sustained hypoxemia in a patient with sickle cell disease and radiographic evidence of restrictive lung disease.

Case Report

A 37-yr-old, 81-kg woman presented with symptomatic chronic cholelithiasis and was scheduled for elective laparoscopic cholecystectomy. She was admitted as an ambulatory patient on the morning of surgery.

Her past medical history was remarkable in that she was homozygous for sickle cell disease (Hb SS) and she presented with sickle cell anemia since childhood. She required several previous hospital admissions because of recurrent painful crises involving the abdomen, lungs, and joints. These crises necessitated frequent blood transfusions. Clinical manifestations of sickle cell disease in this patient included osteomyelitis of the left tibia and avascular necrosis of the left femur, and complications also included difficult venous access. A right-sided hemopneumothorax had previously complicated an attempted central venous cannulation using the right subclavian vein approach. A left arm arteriovenous fistula was created surgically to facilitate vascular access. Her medications at the time of admission included daily oral folate and meperidine, as needed for pain relief.

Physical examination revealed a heart rate of 82 bpm, supine arterial blood pressure of 120/75 mm Hg, and a grade II/VI systolic ejection murmur that was audible along the left sternal border. Auscultation of the lungs was unremarkable. Preoperative hemoglobin was 9.7 g/dL and hematocrit was 29.6%. The remainder of the hematologic assessment, coagulation screen, renal and liver function

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tests, and serum electrolytes were within normal limits. The admission electrocardiogram revealed sinus rhythm and left ventricular hypertrophy. Roentgenographic examination of the chest revealed small lung volume, extensive interstitial infiltrative changes, and biconcave vertebrae with osseous changes of the right fifth rib. Arterial blood gas analysis and pulmonary function tests were not obtained before surgery, and a preoperative blood transfusion regimen was not used.

In the operating room, routine monitors (electrocardiogram, automated noninvasive blood pressure sphygmomanometer, precordial stethoscope, and oximeter) were placed, and an 18-gauge indwelling catheter was inserted in the right internal jugular vein because of limited peripheral venous access. Fentanyl 100 μg was administered intravenously before induction of anesthesia. A heart rate of 82 bpm, arterial blood pressure of 120/70 mm Hg, and oxygen saturation of 97%, while breathing room air, were documented before induction of anesthesia.

Anesthesia was induced with thiopental 4.0 mg/kg IV, and vecuronium 0.1 mg/kg IV was administered to facilitate tracheal intubation. Anesthesia was maintained with 0.5%–1.0% end-tidal isoflurane and nitrous oxide in 50% oxygen, with incremental bolus (1–2 μg/kg) doses of intravenous fentanyl. After induction of anesthesia, urinary bladder catheter and nasogastric tubes were inserted. Intraoperative monitoring included continuous electrocardiogram (leads II and V_5), pulse oximetry, end-tidal capnography, neuromuscular function, inspired oxygen fraction, peak airway pressure, esophageal temperature, and urinary output.

With the patient in a steep Trendelenburg position, a Veress needle was introduced into the peritoneal cavity through an infraumbilical incision, and carbon dioxide was insufflated to an intraabdominal pressure of 15 mm Hg via an electronic variable-flow, pressure-controlled insufflator. Systemic blood pressures ranged between 100 and 140 mm Hg systolic, 70 and 90 mm Hg diastolic, and pulse rates varied between 90 and 100 bpm; arterial oxygen saturations of 97%–99% and peak airway pressures of 25–30 cm H_2O were recorded. Intermittent positive pressure ventilation (IPPV) was employed using an Ohmeda 7810 ventilator, with an inspiratory flow rate of 25 L/min and an inspiratory-to-expiratory (I:E) ratio of 1:2. Minute ventilation was adjusted to maintain end-tidal carbon dioxide tension between 30 and 35 mm Hg.

The patient's position was changed to a steep 20° reverse Trendelenburg with left lateral tilt. During the ensuing 20 min, as the fundus of the gallbladder was retracted and the cystic duct and artery were mobilized, arterial oxygen saturation progressively declined to 86%, with a gradual increase in peak airway pressure to 50 cm H_2O. Nitrous oxide administration was discontinued and IPPV with a fractional inspired oxygen tension (FIO_2) of 1.0 plus 5 cm H_2O positive end-expiratory pressure (PEEP) was commenced. Heart rate, arterial blood pressure, and end-tidal carbon dioxide tensions were essentially unchanged, and no twitch responses were elicited on neuromuscular function monitoring after supplemental vecuronium administration. Chest movement was symmetrical bilaterally, and auscultation of the lungs revealed no abnormality. Access limitations precluded radial artery cannulation for arterial blood gas analysis. Despite IPPV with an FIO_2 of 1.0 and a minute ventilation of 8 L, arterial oxygen saturation of 85% persisted for 5 min. No changes were made in the inspiratory flow rate or the I:E ratio. Because of sustained and moderately severe hypoxemia in a patient homozygous for sickle cell disease, the surgical team was requested to convert the procedure to an open cholecystectomy. The patient was placed in a supine position and the intraabdominal carbon dioxide was vented. Arterial oxygen saturation promptly increased to 99% and peak airway pressure decreased to 25–30 cm H_2O.

The remainder of the open cholecystectomy procedure was uneventful. Neuromuscular block was reversed with 2.5 mg neostigmine plus 0.4 mg glycopyrrolate IV, and the trachea was extubated once the patient was fully awake and following commands. Arterial oxygen saturation >97% was documented in the postanesthesia recovery room throughout the patient's stay. The postoperative chest radiograph was essentially unchanged compared with the preoperative film. The postoperative period was complicated by the development of a painful abdominal Hb SS crisis 3 days after surgery, which required transfusion of 2 U of packed red blood cells. The patient was discharged 6 days after surgery.

Discussion

We report the first case of conversion from laparoscopic to open cholecystectomy because of sustained intraoperative hypoxemia and high airway pressures in a patient with sickle hemoglobinopathy and interstitial lung disease. We speculate that hypoxemia in this case may have resulted from ventilation-perfusion mismatch and intrapulmonary shunting secondary to preoperative decreased lung volumes and extensive interstitial lung disease, coupled with a further decrease in functional residual capacity induced by the creation of the pneumoperitoneum. A list of the factors that could be implicated in the development of intraoperative hypoxemia in this case is included in Table 1.

The preexisting infiltrative lung disease may have contributed to the development of intraoperative hypoxemia in this case. Sickle cell chronic lung disease (SCLD) has been reported to be a prime contributor to mortality in young adults with sickle cell hemoglobinopathy (13). Both perfusion and diffusion defects have been demonstrated, with generalized pulmonary fibrosis and disabling restrictive respiratory failure (14). Powars et al. (15) defined four stages of SCLD based on pulmonary function tests, chest roentgenograms, arterial blood gas analysis, and noninvasive cardiac studies. Patients, similar to the one reported here, were categorized as stage 2, based on chest radiologic findings of diffuse parenchymal fibrosis. Case-control analysis showed that the significant risk factors associated with the disease were

Table 1. Intraoperative Hypoxemia During Laparoscopic Cholecystectomy—Differential Diagnosis

- Pre-existing conditions
  - Cardiopulmonary disease
  - Morbid obesity
- Hypoventilation
  - Patient position
  - Pneumoperitoneum
  - Endotracheal tube obstruction
  - Inadequate ventilation—spontaneous/controlled
- Intrapulmonary shunting
  - Reduced FRC (pneumoperitoneum induced)
  - Endobronchial intubation
  - Pneumothorax
  - Emphysema—mediastinum/subcutaneous
  - Bowel distention (N_2O induced)
  - Pulmonary aspiration of gastric contents
- Reduced cardiac output
  - Hemorrhage—trochar injury
  - Inferior vena caval compression
  - Impaired venous return—pneumoperitoneum
  - Dysrhythmias—hypercarbia/volatile anesthetic agents
  - Myocardial depression—drug-induced/acidosis
  - CO_2 venous embolism

FRC, functional residual capacity.

the total number of acute chest syndrome events in an individual before the onset of SCLD and the presence of sickle cell crises marked by chest pain and aseptic necrosis. Temporal clustering of acute chest syndrome episodes frequently heralds the onset of SCLD.

Intraoperative hypoxemia may have been caused by a reduction in alveolar oxygen tension, an increased alveolar/arterial oxygen tension difference, or a reduction in cardiac output, singly or in combination. A reduction in alveolar oxygen tension may be caused by reduced or absent inspired oxygen concentration and decreased alveolar ventilation. Hypoxemia due to mechanical failure of the oxygen supply system or the anesthetic machine, disconnection of the breathing system from the oxygen supply, and inadvertent excess nitrous oxide administration were all excluded by inspection of the inspired oxygen analyzer, by checking the anesthetic breathing circuit, and by auscultation of the lungs. Kinking of the endotracheal tube, blockade by secretions, or a herniated or ruptured endotracheal tube cuff were excluded by confirmation of symmetrical chest movements and normal breath sounds.

An increased alveolar/arterial oxygen tension difference may lead to intraoperative hypoxemia. This will be most commonly associated with increased intrapulmonary shunting and decreased mixed venous oxygen tension. Inadvertent endobronchial intubation because of frequent positional changes from the Trendelenburg position to the reverse Trendelenburg and left lateral tilt position were excluded by clinical assessment. A tension pneumothorax has been reported as a complication during laparoscopic cholecystectomy after trochar insertion and intraperitoneal carbon dioxide insufflation (16). A congenital defect of the diaphragm (patent pleuroperitoneal canal) through which the insufflated gas passes into the thoracic cavity has been suggested as the underlying mechanism (17). A pneumothorax was excluded by clinical evaluation during surgery and chest x-ray after surgery.

A reduction in functional residual capacity relative to closing volume may be associated with the development of intraoperative atelectasis and intrapulmonary shunting. These changes may be associated with general anesthesia because of a variety of factors: (a) cephalad shift of the diaphragm associated with supine position (18); (b) loss of inspiratory muscle tone; (c) appearance of end-expiratory muscle tone in the abdominal expiratory muscles; (d) changes in intrathoracic blood volume associated with induction of anesthesia (19); and (e) influence of muscle relaxants on diaphragmatic excursion (20). The reduction in functional residual capacity associated with general anesthesia may be compounded by the carbon dioxide-induced pneumoperitoneum during laparoscopic cholecystectomy. A reduced cardiac output secondary to pneumoperitoneum-induced reduction in venous return or drug-induced myocardial depression may have reduced mixed-venous oxygen tension. The larger the intrapulmonary shunt and the greater the reduction in mixed-venous oxygen tensions, the greater the reduction in the arterial partial pressure of oxygen.

A number of case reports have described acute hypotension, hypoxemia, and cardiovascular collapse associated with laparoscopy (21, 22). Postulated causes included hypercarbia due to hypoventilation or absorption of carbon dioxide from the peritoneal surface, inducing dysrhythmias, especially if the myocardium is sensitized by volatile anesthetic agents; reflex increase of vagal tone due to excessive stretching of the peritoneum; compression of the inferior vena cava leading to decreased cardiac output; hemorrhage; and venous gas embolism. The clinical conditions associated with venous carbon dioxide embolism during laparoscopy have been described (23,24). The authors suggested that carbon dioxide could enter a tributary of the portal system during attempts at establishing the pneumoperitoneum. In this case report, the unchanged heart rate, rhythm, blood pressure, and end-tidal carbon dioxide tension suggest that significant cardiac output reduction or venous gas embolism were unlikely mechanisms of the hypoxemia and high airway pressure. Gastric regurgitation has been reported during gynecologic laparoscopic procedures (25). The prompt improvement in arterial oxygen saturation on venting the intraperitoneal carbon dioxide, the absence of visible gastric contents at the time of tracheal extubation, and the unchanged postoperative chest film make aspiration an unlikely mechanism in this case.

The ventilatory effects of carbon dioxide insufflation during laparoscopic cholecystectomy were prospectively evaluated by Liu et al. (26) in a study of 16 otherwise healthy patients undergoing laparoscopic cholecystectomy under general anesthesia. End-tidal carbon dioxide and $Paco_2$ increased from 31.4 ± 0.7 mm Hg to 42.1 ± 1.6 mm Hg, and from 33.3 ± 0.7 mm Hg to 43.7 ± 1.2 mm Hg, respectively, during the course of the procedure. Arterial pH decreased from 7.43 ± 0.01 to 7.34 ± 0.01, and bicarbonate concentration remained constant. Thirteen of 16 patients required increased minute ventilation to correct the hypercarbia detected by capnography. Wittgen et al. (27) compared the ventilatory effects of laparoscopic cholecystectomy in 20 patients with normal cardiopulmonary status (ASA physical status I) to the ventilatory effects in 10 patients with documented cardiac and pulmonary disease (ASA physical status II and III). Patients with preoperative cardiopulmonary disease demonstrated significant increases in arterial carbon dioxide tensions and decreases in pH compared with patients without underlying disease. Conversion to open cholecystectomy was required in two patients who demonstrated persistent hypercarbia and respiratory acidosis, despite vigorous hyperventilation. The patient in this case report had preoperative radiologic evidence of small lung volumes and extensive interstitial lung disease secondary to long-standing sickle cell disease. The creation of the pneumoperitoneum may have resulted in a critical further reduction in functional residual capacity and an increased intrapulmonary shunt leading to progressive arterial oxygen desaturation, which was refractory to increased minute ventilation, PEEP, and supplemental oxygen administration.

The application of PEEP >5 cm H_2O was considered inappropriate because of development of high airway pressures with the potential for pulmonary barotrauma, decreased venous return, and hypotension. An alternative strategy—inverse ratio ventilation—might have improved gas exchange at lower levels of PEEP and peak distending pressures (28). Inverse ratio ventilation could have been used with volume-cycled ventilation and end-inspiratory pause/decelerating inspiratory flow rate or pressure-controlled ventilation applied with a long inspiratory time. However, adverse hemodynamic effects and gas trapping may have followed these ventilatory interventions. The inability to maintain an arterial oxygen saturation >85% despite an Fio_2 of 1.0 plus 5 cm H_2O PEEP in our patient with sickle cell disease was considered sufficient justification for conversion to an open cholecystectomy. Upon deoxygenation, red blood cells containing Hb S change from a biconcave disc to an elongated crescent-shaped or "sickle"-shaped cell (29). The ability of red blood cells to traverse the microcirculation depends, in large part, on their pliability. As the red blood cell sickles, it becomes rigid, and, as a result, may obstruct capillary blood flow. The deoxygenation of blood from patients with sickle cell disease is associated with a marked increase in viscosity and, in this case, the inability to promptly reverse the arterial hypoxemia was of major concern. Arterial oxygen saturation promptly increased, and peak airway pressures decreased, upon changing to the supine position and after venting the intraperitoneal carbon dioxide.

Table 2 details the indications for conversion from laparoscopic to open cholecystectomy in five recently published series (30–34), in which the conversion rates varied from 1.0% to 6.9%. Experience from several institutions suggests that the incidence of common bile duct injuries may be higher with the laparoscopic procedure, and conversion to open cholecystectomy was usually caused by difficulty in identifying and mobilizing the cystic duct, suspected or confirmed common bile duct injury, uncontrolled bleeding from the cystic artery, acute inflammatory changes, or stones present in the common bile duct. Apart from isolated case reports and letters describing the uneventful anesthetic management of such cases (35–37), the anesthesia literature is conspicuous by the absence of data concerning anesthesia-related complications of laparoscopic cholecystectomy (38).

The role of a preoperative transfusion regimen in reducing the morbidity of cholecystectomy in patients with sickle hemoglobinopathy is speculative and must be balanced by the potential hazards of disease transmission and erythrocyte allosensitization (39). In patients with homozygous sickle cell disease, the erythrocytes may contain 80%–95% Hb S, with the remainder consisting of 5%–20% fetal hemoglobin (Hb F). Protocols have been advocated that include the preoperative transfusion of packed red blood cells with hemoglobin A erythrocytes in Hb SS patients to restore the percentage of Hb S to <45%, as determined by quantitative hemoglobin electrophoresis (40). The rationale for this management is to increase the proportion of normal erythrocytes containing Hb A to a level that will inhibit blockage of the microcirculation by sickling cells. However, the efficacy and safety of transfusion therapy in patients with sickle hemoglobinopathy were questioned in a retrospective study by Bischoff et al. (41). Transfusion therapy was administered preoper-

Table 2. Reported Indications for Conversion From Laparoscopic to Open Cholecystectomy

Authors	Study period	Study design	Location	Institution	Patients	Conversion to open cholecystectomy
Spangenberger et al. (1990) (Reference 30)	1989–90	Retrospective	Cologne, Germany	Teaching	100	1 (1%) 1 Bile duct leak
Peters et al. (1991) (Reference 31)	1989–90	Prospective	Columbus, Ohio	Community	100	4 (4%) 1 CBD injury 1 Uncertain anatomy 2 Acute inflammation
Nathanson et al. (1991) (Reference 32)	?	Retrospective	Dundee, Scotland	Teaching	61	1 (2%) 1 Dilated CBD with stones
Graves et al. (1991) (Reference 33)	1989–90	Retrospective	Nashville, Tennessee	Community	304	21 (6.9%) 6 Acute cholecystitis 6 Chronic scarring 2 R/O CBD injury 1 CBD injury 1 Obesity 1 Benign liver tumor 1 Small intestine injury 1 Carcinoma gallbladder 2 Stone impaction cystic duct
Cuschieri et al. (1991) (Reference 34)	1989–90	Retrospective	European multicenter	Mixed teaching and community	1236	45 (3.6%) 33 Technical difficulties 8 Uncontrolled bleeding 2 CBD injury 1 Rupture empyema 1 Instrument failure

CBD, common bile duct; R/O, rule out.

atively in 48 of the 66 patients reviewed. No significant reductions in postoperative sickling complications and increased morbidity related to transfusion adverse events were reported after preoperative transfusion in patients with preoperative hematocrits of <30%.

Based on the limited data available in the literature, and on our own experience with this procedure, we advocate preoperative arterial blood gas analysis and pulmonary function testing for patients undergoing laparoscopic cholecystectomy in whom respiratory risk factors have been identified on routine preoperative evaluation. In this era of cost containment, these patients may not be suitable for admission on the morning of surgery if such ancillary preoperative investigations are not available at the preoperative screening clinic. If hypoxemia, hypercarbia, or respiratory acidosis are documented by preoperative arterial blood gas analysis or if impaired pulmonary function tests are reported, we would express reservations about proceeding with the laparoscopic, rather than the open, cholecystectomy technique. If surgical management involved the laparoscopic technique, we would advocate radial artery cannulation, in addition to end-tidal carbon dioxide monitoring, to assess the adequacy of oxygenation and ventilation after pneumoperitoneum creation (42). This case and the limited published data (26,27) suggest that restrictive or obstructive lung disease may be relative contraindications to a laparoscopic cholecystectomy technique and that anesthesiologists should have a low threshold for recommending conversion from laparoscopic to open cholecystectomy if problems of high airway pressures or refractory hypoxemia are encountered during surgery.

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An Unusual Presentation of Spinal Cord Tumor After Epidural Anesthesia

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The incidence of backache in the peripartum period is 25%–50% with or without epidural block (1–3). Backache is often attributed to ligamentous strain and managed with the conservative therapy of bed rest and analgesics. However, severe and/or persistent back pain or associated neurologic symptoms may indicate pathology requiring timely intervention for optimal outcome. We report an unusual case of an intradural spinal cord tumor presenting as severe, persistent, back pain after epidural anesthesia for cesarean section. This case is unique because the patient presented with back pain without sensory or motor deficits and because a previous epidural anesthetic complicated the interpretation of the magnetic resonance imaging (MRI) scan.

Case Report

An apparently healthy, 31-yr-old woman with no previous history of back pain underwent a cesarean section for prolonged labor under epidural anesthesia at a referring hospital. After her operation, she experienced intermittent, sharp, nonradiating low back pain that slowly abated until 18 mo later when she underwent her second cesarean section under epidural anesthesia, also at the referring institution. The intense back pain that developed immediately postoperatively required 2 wk of bed rest and analgesics. She denied experiencing any weakness or numbness in the lower extremities at any time, nor did she experience any bowel or bladder dysfunction. When pain was present, it was increased by bending forward, coughing, or sneezing. Neurologic examination was unremarkable. An MRI scan demonstrated an abnormality within the thecal sac posterior to the L-4 and L-5 vertebral bodies not typical for a tumor and more suggestive of a localized intrathecal hematoma or inflammatory process (Figures 1 and 2). The radiologist further suggested that the finding "may represent some type of sequela from the previous spinal [sic] anesthesia such as localized intrathecal hemorrhage."

Persistent symptoms led to a repeat MRI scan 6 mo later, which revealed a well-demarcated intradural tumor extending from the superior vertebral plate of L-4 to the inferior aspect of the L-5 vertebral body (Figures 3 and 4). At this time the patient was transferred to our medical center for treatment. She underwent general anesthesia for L-4, L-5 laminectomy, bilateral L-3 hemilaminotomy, and resection of an intradural mass densely adherent to the cauda equina and the filum terminale extending from L-3 to L-5. A total gross removal was accomplished with preservation of all nerve roots. Pathological review of the surgical specimen revealed a myxopapillary ependymoma. No abnormality was detected in the epidural space. The postoperative course was uncomplicated, with preservation of neurologic function. As ependymomas tend to reoccur after surgery, radiation therapy was begun 1 mo postoperatively. At follow-up 1 yr postoperatively, the patient is asymptomatic with no neurologic deficit.

Discussion

Patients often attribute low back pain after delivery to epidural anesthesia; however, the incidence of low back pain after delivery is unrelated to the use of general, epidural, or pudendal anesthesia (1,3–5). Although most patients with low back pain improve with symptomatic therapy, severe and/or persistent low back pain, such as this patient demonstrated, necessitates consideration of etiologies other than the common musculoskeletal injuries. The differential diagnosis of low back pain is extensive, and includes tumor, infection, herniated disks, spinal stenosis, spondylolisthesis, hemorrhage, and ankylosing spondylitis. Also visceral disease, such as endometriosis or nephrolithiasis, may present with back pain as the chief complaint (6,7). This patient's first MRI scan, demonstrating localized hemorrhage, was interpreted to be a result of recent instrumentation of the subarachnoid space. As the patient did not demonstrate neurologic signs, no further assessment or intervention was performed. Repeat MRI clearly demonstrated intradural tumor. Improved communi-

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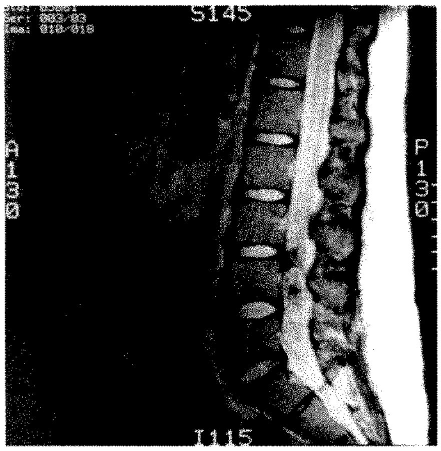

Figure 1. Sagittal MRI slice of lumbar spine with intradural tumor, March 1990.

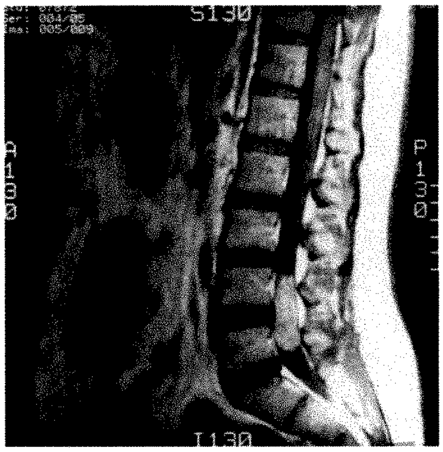

Figure 3. Sagittal MRI slice of lumbar spine with intradural tumor, October 1990.

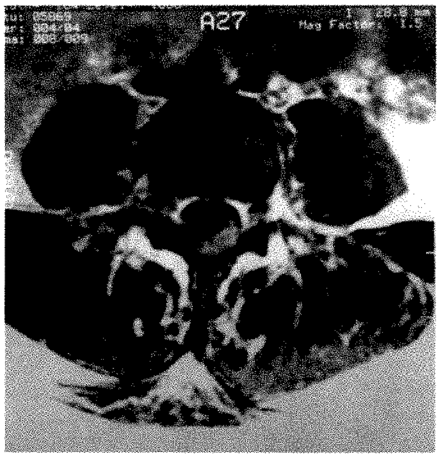

Figure 2. Axial MRI slice, with contrast, of lumbar spine with intradural tumor, March 1990.

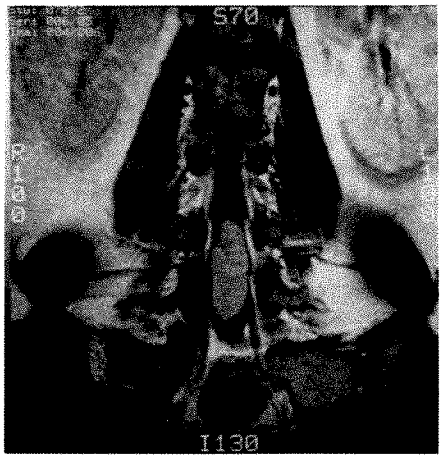

Figure 4. Anterior-posterior MRI slice of lumbar spine with intradural tumor, October 1990.

cation between the anesthesiologist and radiologist in this case may have clarified the misconception that a "spinal" anesthetic was administered to this patient. Clarifying that it was an epidural anesthetic may have led to further evaluation of the intrathecal hemorrhage. Fortunately, in this case, a delay in diagnosis did not result in harm to the patient. Although spinal anesthesia is associated with varying degrees of spinal hemorrhage in up to 0.35% of the cases (8), spontaneous spinal subdural hematoma in the absence of tumor or vascular abnormalities is rare (8,9).

Tumor as a cause of low back pain is uncommon. Deyo and Diehl (10) found a 0.66% incidence in 2000 walk-in patients with low back pain. Symptoms preceded the detection of the tumor by an average of 2 yr. Depending on the location of the tumor, local, segmental, or distant signs and symptoms may be the presenting symptoms. Generalized back pain and dermatomal pain tend to be early harbingers. It is unclear why this patient developed acute severe, low back pain after her first cesarean section. One could speculate that an acute shift in tumor position resulted in neuronal compression and thus the development of low back pain. A shift in tumor position could result from an increase in cerebrospinal fluid pressure secondary to injection of epidural local anesthetic, a change in lumbar alignment secondary to motor relaxation, or a decrease in epidural blood volume after delivery (releasing the inferior vena cava compression caused by the gravid uterus). Intradural tumors occur at an incidence of 3–10 per 100,000 population. Approximately 90% of all intradural tumors are benign and potentially resectable. Myxopapillary ependymoma is almost exclusively a tumor of the cauda equina that occurs most often in the fourth decade. The tumor may infiltrate nervous tissue and bone but rarely metastasizes. The prognosis is excellent when the tumor can be completely removed surgically (11).

Usubiaga (12) summarized six case reports of serious sequelae of epidural anesthesia in the presence of occult metastatic spinal osseous tumors. Hirlekar (13) reported paraplegia after epidural anesthesia in the presence of extradural spinal cord tumor. Hirsch et al. (14) used epidural anesthesia for management of labor pain in a patient with an undiagnosed cervical spinal arteriovenous malformation. It was not until 4 wk later that progressive paraplegia developed. Our case is the only one in which an intradural spinal tumor presented in the peripartum period, in association with epidural anesthesia.

The decision to proceed with epidural anesthesia in the presence of low back pain is an individual, patient-physician decision. Most difficulties in identifying the epidural space or threading the catheter are technical problems confronting the anesthesiologist. Renck and Torbergsen (15) have described the findings that might occur when an epidural catheter is inserted in the presence of a spinal cord tumor. There may be resistance to introduction of the catheter, severe paresthesia in one spinal nerve, or a bizarre distribution of sensory analgesia. Difficulty in establishing epidural anesthesia was not noted with our patient. Fortunately, our patient did not suffer major neurologic sequelae after instrumentation of the epidural space. If lumbago or other symptoms possibly related to anesthetic involvement develop, the patient should undergo appropriate evaluation when such symptoms are unrelieved by symptomatic therapy. Failure to detect tumor of this region promptly may result in inadequate resection of the lesion or permanent neurologic deficit.

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Transesophageal Echocardiographic Detection of a Right Atrial Thrombus Around a Pulmonary Artery Catheter

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Transesophageal echocardiography (TEE) is of substantial value in the diagnosis of cardiac mass lesions (1). Because it is unacceptable that the surface of intravascular catheters induce thrombus formation and embolization, surface heparinization has become standard practice for pulmonary artery catheters (PACs). We recently performed TEE for postoperative assessment of right and left ventricular function, during which time a thrombus was found around a PAC in the right atrium.

Case Report

A 68-yr-old woman with a history of asthma and a previous cataract operation was scheduled for coronary revascularization for two-vessel disease. Left ventricular contractility appeared to be normal on preoperative angiography. (Left end-diastolic pressure was 8 mm Hg before and 16 mm Hg after contrast injection.) A heparin-coated, 7.0F thermodilution PAC (AMC Thromboshield, Baxter Edwards Swan-Ganz) was inserted via the right internal jugular vein through an 8.0F introducer sheath with a side port and a hemostatic valve. During cardioplegic myocardial arrest, the left anterior descending artery was bypassed with the left mammary artery, and a venous graft was implanted on the right coronary artery. Because the first attempt at weaning from extracorporeal circulation was unsuccessful owing to low cardiac output, one more venous graft was performed on a diagonal branch. Immediately after bypass, the patient was in sinus rhythm and required dopamine (5–10 $\mu g \cdot kg^{-1} \cdot min^{-1}$) as inotropic support. At the end of surgery, she had bilateral unreactive, wide pupils but appeared to wake up 4 h later. Myocardial enzymes were elevated the next morning (myocardial fraction of creatinine phosphokinase was 66 IU/L and glutamic oxaloacetic transaminase was 115 IU/L [normal value <40]), and there was electrocardiographic evidence (significant ST-segment elevation in the corresponding leads) of septal myocardial infarction. Transesophageal echocardiography was performed on the second postoperative day because of persisting low cardiac output with pulmonary hypertension (peak systolic pressure 60 mm Hg) that had been present since termination of cardiopulmonary bypass. Apart from a limited area of posteroseptal and anteroseptal akinesia and spontaneous contrast in the right cavities indicative of decreased blood flow, a 2 × 3-cm echodense mass in connection with the PAC was noted in the right atrium, as shown in Figure 1. The mass was fairly mobile and entered the right ventricle through the tricuspid orifice during diastole and returned to the right atrium during systole. The patient did not have atrial fibrillation. Although a thrombopenia of 28,000/mm^3 existed, it was assumed that the irregular lobulated border of this mass was a thrombus associated with the indwelling PAC. Because the pulmonary hypertension could be explained by recurrent pulmonary emboli, our patient underwent heparinization with 25,000 U/day. Thrombolysis was considered contraindicated in this patient. Meanwhile, a norepinephrine infusion was started to maintain an adequate mean arterial blood pressure. A hemothorax on the left side had to be evacuated. Two days later, repeat TEE revealed minor reduction of this mass lesion, which was still situated in the right atrium and attached to the PAC. The PAC with the thrombus sticking to it was temporarily left in place. We believed that the presence of the PAC prevented the entire large thrombus from migrating into the lungs and causing a sudden life-threatening pulmonary embolism. On the seventh postoperative day, the thrombus was resolved to a diameter of 5 mm and appeared as a "string" thrombus in the superior vena cava when the PAC was gently drawn back. It was then decided to remove the flow-directed PAC and the sheath as a unit and to discontinue heparinization. The tip of the catheter was cultured, and there was no remaining clotting visible on the PAC. Over several days, the patient was gradually weaned from mechanical ventilation and was discharged from the intensive care unit on the 16th postoperative day. Eventually, she was discharged to a long-term care facility after a hospitalization of 3 mo for dyspnea during the night and left pleural effusions.

Discussion

A mass in the right atrium was inadvertently detected in a postoperative patient. In such a case, one should

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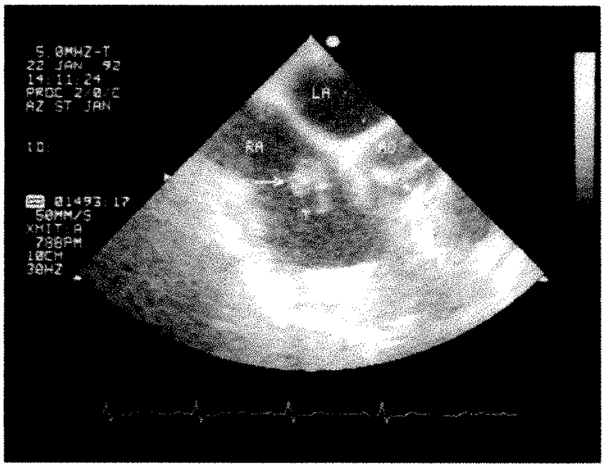

Figure 1. Basal short-axis view at the level of the atria and the aorta in diastole as seen by transesophageal echocardiography (TEE). In the right atrium (RA), a mass (T) is seen in close proximity to the pulmonary artery catheter (*arrow*). LA, left atrium; AO, aorta.

carefully differentiate among Chiari's network and eustachian valves (both normal variants), a myxoma, other tumors, and thrombi. Echocardiographically, the mass had thrombuslike characteristics: laminated appearance, irregular or lobulated borders, and lack of obvious tumor features, such as a narrow stalk or origin from atrial septum (1). Recent reports indicate that TEE is superior to transthoracic echocardiography in diagnosis of an atrial mass and assessment of its size and mobility (2,3). Although it is impossible to prove that a thrombus was induced by the PAC, it is highly probable for the following reasons: first, the mass moved toward the superior caval vein when the catheter was retracted; second, according to a subsequent checkup by our pneumologists, there was no longer evidence of pulmonary emboli, as would be expected if the clot originated in the peripheral venous circulation; and third, the cardiac surgeons who routinely examined the patient's legs preoperatively had no reason to suspect a deep venous thrombosis.

Local thrombus formation around a PAC in the right side of the heart and in the internal jugular or subclavian vein has been described previously (4). In one autopsy study, there were mural thrombi in the chambers on the right side of the heart in approximately one-third of patients with PACs (5). By contrast, a review of PACs in 6245 patients revealed the recovery of a blood clot (weighing ~50 g) in only one patient (6). Those authors advise aspiration on the side port of the sheath during its removal to retain any clot and to prevent its embolization. The rapidity and degree of clot formation depend on the patient's cardiac output and coagulation status, the physician's technique, the length of time the catheter is left in place, and the characteristics of the catheter.

Despite heparin coating, peroperative full heparinization, postoperative thrombopenia, and the absence of atrial fibrillation, clot formation around a PAC may have occurred in this patient. Partial stagnation of blood, together with turbulent flow in the cavities on the right side of the heart during extracorporeal circulation, may have contributed to this phenomenon. Many venous thromboses are not clinically evident; therefore they may be undetected unless they occur suddenly or are sought by radionuclide venography, radiopaque injection, or sonography (7).

Because of the TEE findings, heparinization was instituted in this patient. As a consequence, pulmonary angiography would not have influenced treatment and was not performed. Moreover, easy accessibility of TEE in the operating room and intensive care unit offers distinct advantages over the standard diagnostic techniques (perfusion scanning, pulmonary angiography). In selected cases (e.g., suspected massive pulmonary embolism), TEE may become the procedure of choice (8,9).

Heparin-coated equipment has been used in combination with high-flow cardiopulmonary bypass without systemic heparinization in canine experiments (10). Heparin-coated surfaces belong to the group of ionic-bound heparins and have the advantage that they can be applied to a multitude of surfaces, in contrast to the covalently bound heparins (heparin bonding), which are more limited in this regard. However, the latter show superior retention. Both heparin bonding and heparin coating have been introduced as new approaches to reduce catheter-induced embolization (11).

In conclusion, TEE was not only valuable in the noninvasive evaluation of a postoperative low-output syndrome and the early detection of an intracardiac lesion, most likely a right atrial clot induced by a PAC, but it also influenced clinical decisions (i.e., heparinization and timing of removal of the PAC).

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Intraoperative Exacerbation of Parkinson's Disease

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Parkinson's disease afflicts approximately 1% of the population over 50 yr old (1). Its associated muscle tremors and rigidity are progressive and become severe enough to debilitate many patients. We summarize a case of advanced Parkinson's disease with an intraoperative exacerbation during regional anesthesia. A discussion of its consequences and treatment follow.

Case Report

A 73-yr-old man with Parkinson's disease required anesthesia for repair of a large recurrent left inguinal hernia. His Parkinson's disease was treated with carbidopa 25 mg and levodopa 100 mg five times a day; amantadine 200 mg three times a day; and selegiline 5 mg each day. Levodopa was administered every 4 h while awake. Delaying or omitting a single dose resulted in severe generalized body tremors and rigidity. He also suffered from congestive heart failure for which he received lanoxin 0.125 mg each day and isordil 20 mg three times a day, as well as sick sinus syndrome for which he had received a permanent pacemaker. Previous anesthetics were limited to one general anesthetic for left inguinal hernia repair and one spinal anesthetic for transurethral resection of the prostate. There were no known anesthetic complications.

He had taken his usual morning medications 2 h before the planned surgery. Physical examination 1 h before surgery revealed masklike facies and poor facial expressions. No bradykinesia or resting tremor were noted. There were no active signs and symptoms of congestive heart failure nor sick sinus syndrome.

No sedative premedication was given. Field block anesthesia was feared to be inadequate for this large, recurrent hernia and therefore was not performed. Spinal anesthesia was agreed to, and the patient was brought to the operating room where his vital signs were an arterial blood pressure of 140/90 mm Hg; heart rate of 70 bpm with a paced rhythm; respiratory rate of 16 breaths/min; and arterial oxygen saturation of 96% while breathing room air. Hyperbaric bupivacaine, 12 mg, plus 10 μg of fentanyl were injected into the cerebrospinal fluid at the L4–5 interspace. Ten minutes later, a T-9 level was achieved and vital signs were essentially unchanged from initial recordings. One hour after initiating spinal anesthesia, and approximately 45 min into the operation, a prominent artifact emerged on the electrocardiogram, which resembled coarse ventricular fibrillation (Figure 1). This event occurred approximately 5 h after his last levodopa dose. The patient remained awake and alert. Arterial blood pressure, heart rate, respiratory rate, and oxygen saturation were essentially unchanged. Examination of the patient's chest and upper extremities revealed fine tremors that progressed to more gross tremors over a 10-min period. The patient reported subjective feelings of discomfort. The constellation of signs and symptoms was similar to manifestations of his Parkinson's disease. Levodopa and carbidopa were given orally with a sip of water while surgery continued. Motor activity and the subjective feelings of discomfort resolved approximately 20 min after initiating therapy. Surgery proceeded during the entire episode and ended shortly after tremors ceased.

In the recovery room, the patient admitted that he would occasionally self-administer additional levodopa without his neurologist's knowledge and that the five times a day dosing schedule had not been as effective as it was initially.

Discussion

The etiologies of Parkinson's disease include carbon dioxide or manganese poisoning; butyrophenone, phenothiazine, or reserpine treatment; central nervous system trauma (1); central nervous system tumors; viral encephalitis (2); and arteriosclerosis (3). Pathophysiologically, Parkinson's disease represents a relative imbalance between dopamine's inhibitory effects and acetylcholine's excitatory properties in the basal ganglion (1). The resultant extrapyramidal stimulation predisposes to bradykinesia, tremor, rigidity, and postural instability—the hallmarks of Parkinson's disease (4).

Treatment goals are to establish proper balance between central dopaminergic and cholinergic activity. Patients with mild disease often receive relief from rest tremors and dystonia with anticholinergics such as trihexyphenidyl and benzotropine (5). Diphenhydramine, an antihistamine possessing central anticholinergic effects (6), is sometimes useful in mild disease. Amantadine, a dopamine agonist, is occasionally helpful for early-stage tremors (1,3).

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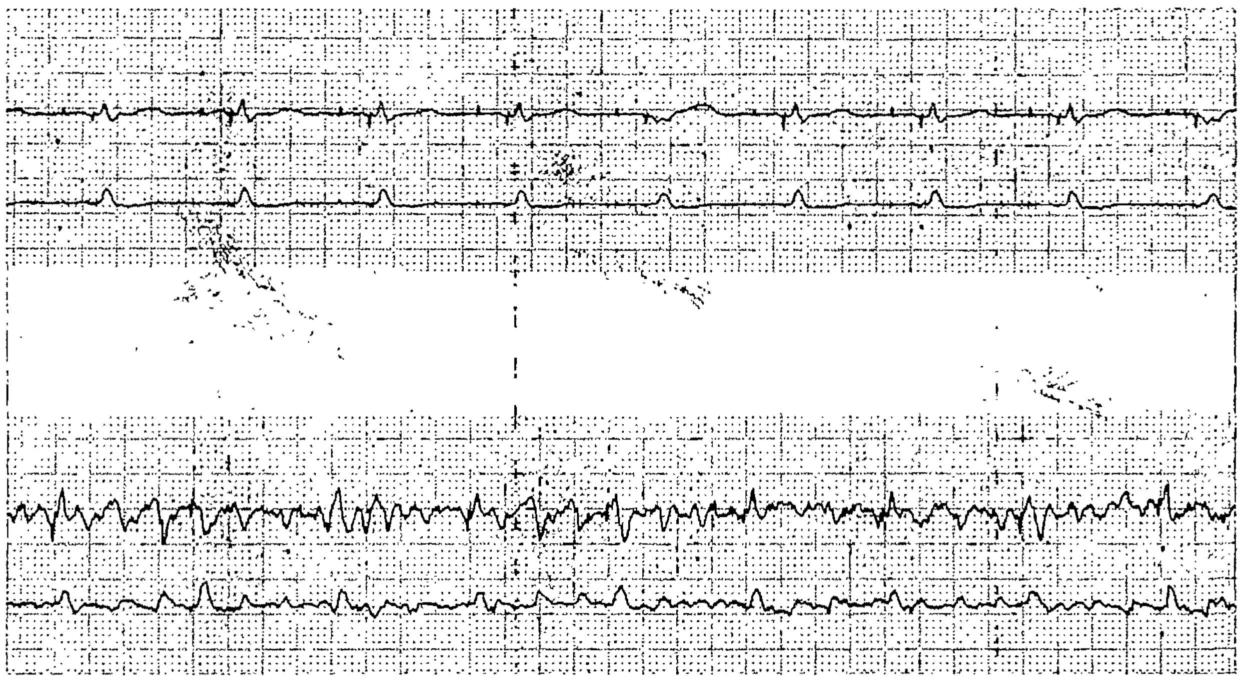

Figure 1. *Upper strip* represents patient's normal paced rhythm. *Lower strip* demonstrates the coarse ventricular fibrillation pattern.

More advanced disease is treated with levodopa, which crosses the blood-brain barrier and reacts with dopa-decarboxylase to form dopamine. To reduce dopamine's peripheral effects such as nausea, orthostatic hypotension, and arrhythmias, levodopa is usually combined with carbidopa, a dopa-decarboxylase inhibitor that does not cross the blood-brain barrier. This combination enhances brain dopamine levels while reducing systemic symptoms (7). Chronic levodopa treatment may result in requirements for increased dosing frequency (3,5). In such cases, bromocriptine, a postsynaptic dopamine receptor agonist, may be useful (5). Selegiline, a monoamine oxidase inhibitor type B (8,9), has been used to slow the progress of Parkinson's disease (10,11).

Most authors recommend continuation of therapy perioperatively (12–14) to avoid laryngospasm (4), aspiration pneumonitis (15–17), obstructive lung disease (17,18), hallucinations (5), and violent tremors—the recognized complications of Parkinson's disease. Patients with Parkinson's disease appear to be at increased risk for these problems in the perioperative period. Violent tremors and rigidity on emergence may also be attenuated or abolished by continuing anti-Parkinson's disease treatment through the perioperative period (13,14). Our patient complied with this recommendation, but due to a delay in the time of surgery, his signs and symptoms recurred intraoperatively. Drugs known to exacerbate extrapyramidal stimulation such as droperidol (19), phenothiazines (20), metoclopramide (20), and reserpine (1) were not administered.

Manifestations began with fine skeletal muscle tremors that were grossly unrecognizable, but were revealed by the electrocardiogram monitor. A coarse fibrillatory pattern was displayed. The initial response to perform electrical defibrillation would have been unnecessary and potentially deleterious. Further investigation revealed arterial blood pressure, palpable pulses, respiratory rate, oxygen saturation, and mental status that were all normal for this particular patient. Fine skeletal muscle tremors produced the observed electrocardiogram pattern. This quickly progressed to a clinically severe episode of tremors and rigidity.

In the absence of parenteral anti-Parkinson's disease medications that are effective in advanced cases, we elected to treat with the "per os" form of the drug and accept the prolonged onset time. Treatment with intravenous atropine was considered but rejected because of the increased risk of tachyarrhythmias in a patient with preexisting sick sinus syndrome, congestive heart failure, and elevated systemic dopamine activity from chronic levodopa, amantadine, and selegeline ingestion. Furthermore, atropine is not known to be effective for the treatment of advanced disease. Diphenhydramine and benztropine had previously failed to relieve this patient's manifestations.

Despite suggestions to stop monoamine oxidase inhibitors (MAOIs) 3 wk before anesthesia (21–24), this patient was continued on his therapy through the morning of surgery. Many patients receiving such drugs up to the time of surgery have been anesthetized without significant complications (8). This patient's MAOI, selegiline (L-deprenyl, phenethylamine), has been used for treatment of Parkinson's disease in the United States since 1989. Selegiline is an MAOI type B, which prevents dopamine degradation and has little or no effect on epinephrine or norepinephrine (25). Although metabolized to amphetamines, there is hope that selegiline will produce less sympathetic overactivity than previous MAOIs (26,27). There is no information regarding the interaction of selegiline and anesthetics.

Postoperative ileus represents a serious problem for patients with severe Parkinson's disease. Presently available parenteral medications such as diphenhydramine and benztropine are oftentimes inadequate to treat advanced disease. Parenteral forms of levodopa are only available experimentally, as of this writing. Lisuride (2,7), a dopamine agonist, is available parenterally in Europe, but not in the United States. Levodopa is absorbed from the proximal small bowel (28,29) and therefore is useless as a suppository. Absorption occurs rapidly from the gastrointestinal tract and can be used in many post-laparotomy patients. For those patients in whom intestinal absorption does not take place, only diphenhydramine and benztropine are available for Parkinson's disease treatment in the United States.

This case report highlights several new aspects of perioperative care for patients with advanced Parkinson's disease. Skeletal muscle activity mimicking ventricular fibrillation has been reported previously in anxious and shivering patients (30). However, Parkinson's disease has never before been documented as a specific disease entity that predisposes to this problem. Heightened awareness of the potential for artifactual electrocardiographic representations of ventricular fibrillation should help prevent unnecessary and potentially dangerous electrical defibrillation. Additionally, skeletal muscle activity progressing to rigors can hinder the quality of surgical repair and prolong the operating time.

Previous recommendations for perioperative treatment have not emphasized the need for synchronizing levodopa administration with the beginning of anesthesia and surgery. Based on the 20-min onset time observed in this patient and the documented 30-min to 2-h time to peak plasma levels (31), we recommend administration of oral levodopa approximately 20 min before the start of anesthesia. Such coordination of drug dosing should provide maximal intraoperative and postoperative protection from Parkinson's disease exacerbations.

When necessary, oral levodopa can be administered intraoperatively and postoperatively to control Parkinson's disease manifestations.

Regional techniques are preferable to general anesthesia methods. Regional anesthesia allows for communication of the subjective feelings accompanying Parkinson's disease attacks, thereby prompting earlier treatment. The muscle-relaxing effects of some general anesthetics and neuromuscular blockers will probably mask the myopotentials, which were the first sign of exacerbation in this patient. Consequently, residual general anesthesia or neuromuscular blocker may delay diagnosis and treatment. The high incidence of nausea and vomiting associated with general anesthesia prevents effective administration of oral medications.

Patients with advanced Parkinson's disease are at risk for exacerbations in the perioperative period. These exacerbations place them in jeopardy for unnecessary electrical defibrillation in addition to previously described complications. Oral levodopa should be administered approximately 20 min before inducing anesthesia and may be repeated intraoperatively and postoperatively in many patients. Regional anesthesia may be preferable to allow for communication of the patient's subjective feelings.

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Intraoperative Hypertension During Surgical Excision of Neuroblastoma

Case Report and Review of 20 Years' Experience

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Neuroblastomas and pheochromocytomas are derived from neural crest tissue, and both synthesize and release catecholamines (1–3). The ability of pheochromocytomas to produce life-threatening cardiovascular instability before and during surgical removal is well recognized and reviewed in the anesthesia literature (4–7). Published information concerning anesthetic experience with neuroblastoma is restricted to scattered reports of preoperative and intraoperative cardiovascular instability (8–11), including one report of an intraoperative death (12) with an accompanying general description of the anesthetic management for neuroblastoma (13). The incidence of cardiovascular instability during neuroblastoma resection has not been documented previously.

The following case of an infant with a mediastinal neuroblastoma illustrates that significant tachycardia, hypertension, and catecholamine elevation may accompany surgical excision of this tumor. This case prompted a review of the anesthetic experience with this disease in our institution over the past 20 yr.

Case Report

A 4-mo-old girl presented with a 1-mo history of episodes of diaphoresis, agitation and pallor occurring about every other day and lasting several hours. She had been a full-term infant with an otherwise unremarkable past medical history.

On admission to the hospital, the child appeared to be well and without acute distress. Vital signs were temperature 36.3°C, heart rate (HR) 132 bpm, arterial blood pressure (BP) 83/50 mm Hg, weight 5.4 kg, and length 64.5 cm. Serum electrolytes were normal and the hematocrit was 34%. The electrocardiogram was unremarkable, and the chest radiograph revealed a mediastinal mass that was shown by computed tomography to be a left posteromedial mediastinal mass causing displacement of the trachea.

Soon after admission, episodes of diaphoresis and agitation were observed along with increased BP (maximum 164/92 mm Hg) and HR (maximum 162 bpm). Urine analysis demonstrated elevated concentrations for several catecholamines: vanillylmandelic acid 107 mg/g creatinine (normal 5.1–16.3 mg/g creatinine); homovanillic acid 121 mg/g creatinine (normal 6–30 mg/g creatinine); and norepinephrine 162 µg/24 h (normal 7.2–14 µg/24 h). Serum concentrations of epinephrine, norepinephrine, and dopamine were also elevated (Table 1). A bone scan showed uptake at the tumor site only. Initially, the hypertensive episodes were treated with nifedipine (2.5 mg orally) as needed. Two days after admission, treatment with parenteral hydration and phenoxybenzamine (0.2 mg·kg^{-1}·day^{-1}) was instituted, and phenoxybenzamine was increased to a maximum of 1.7 mg·kg^{-1}·day^{-1} over 10 days until the episodes of diaphoresis were eliminated and hypertension was controlled.

Two weeks after admission, the patient was brought to the operating room for thoracotomy and tumor excision. Preoperative BP was 95/45 mm Hg, HR 115 bpm, weight 6.4 kg. Serum electrolytes remained normal and the hematocrit was 32%. After sedation with intravenous thiamylal, routine noninvasive monitors were applied and an arterial catheter was inserted. Anesthesia was induced with oxygen and isoflurane, and the trachea was intubated without difficulty while the patient was breathing spontaneously. Central venous and urinary catheters were then placed. Anesthesia was maintained with oxygen, air, isoflurane (0.4%–0.5% end-tidal), fentanyl, and vecuronium. The anesthetic course was uneventful until tumor manipulation, which resulted in transient but distinct hypertension and tachycardia (BP increased from 80/40 to 135/80 mm Hg, HR increased from 120 to 140 bpm); the hypertension was controlled with intravenous sodium nitroprusside. The tumor was a well-encapsulated, 4–6-cm mass that was easily removed except for a small residuum that extended

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Table 1. Serum Catecholamine Concentrations

	Epinephrine (NL <90 pg/mL)	Norepinephrine (NL <600 pg/mL)	Dopamine (NL <135 pg/mL)
Admission	370	15,869	248
Preoperative	<20	195	20
Tumor manipulation	104	35,511	<10
Postoperative	344	367	15

NL, normal.

into the second intercostal space. Estimated blood loss for the procedure was 50 mL, and fluid losses were replaced with the intravenous administration of 350 mL of crystalloid solution. After tumor excision, vital signs remained stable. At the termination of the procedure, the infant was awakened and her trachea extubated without complication; no tachycardia, hypertension, or hypotension occurred throughout the postoperative period.

Pathologic examination confirmed the diagnosis of stage II neuroblastoma. Sequential determinations of serum catecholamines in the perioperative period demonstrated a marked elevation of the serum norepinephrine concentration at the time of tumor manipulation and a return to baseline postoperatively (Table 1). The patient has been followed up without additional therapy and has no evidence of recurrent disease 16 mo postoperatively.

Methods

We reviewed the hospital records of 127 children who underwent resection of neuroblastoma at Children's Hospital and Medical Center, Seattle, Washington, between January 1971 and January 1991. Nineteen children underwent biopsy of tumor only and their records were deleted from further analysis. The records of the remaining 108 children were reviewed for preoperative symptoms, HR, BP, and urine or serum catecholamine levels; type of surgical procedure and anesthetic management; intraoperative HR and BP, including maximum sustained BP (recorded at two or more consecutive 5-min intervals) during tumor removal and minimum sustained BP after tumor removal; and final histologic diagnosis. Preoperative BP was considered to be elevated if it was greater than two standard deviations above the mean for age (14). Intraoperative BP and HR were considered to be significantly elevated if they were ≥25% above their postinduction values, and intraoperative BP was considered to be significantly reduced if it was ≤25% of the postinduction value.

Results

There were 55 male and 53 female patients with an average age at the time of surgery of 2.6 yr (range 4 days to 14 yr). Twenty-seven children were asymptomatic and were discovered to have a mass on routine fetal or postnatal examination; 19 children presented with nonspecific symptoms; and 53 presented with symptoms or signs directly related to the mass effect of the tumor. Only nine of the children (8% of the total study population) had a history of symptoms or signs suggestive of increased catecholamine secretion, including flushing, diaphoresis, diarrhea, and hypertension. Two of these nine children had a well-documented history of hypertension, including the child reported here. Fifteen other children with no history suggestive of increased catecholamine secretion had mildly elevated resting systolic BPs on admission to the hospital. Of the 94 children who had preoperative determination of urine and/or serum catecholamines, 81 had elevated levels. Eight of the nine symptomatic children had preoperative catecholamine determinations, all of which were elevated. Thirteen of the 15 children with incidental increased BP on admission had preoperative catecholamine determinations, all of which were elevated. None of the children except the one reported here received antihypertensive therapy preoperatively.

Surgical resection of tumor was preceded by chemotherapy and/or radiation therapy in 36 of the children. Tumor sites were neck (2), thorax (27), abdomen (74), and spinal cord (5). The average duration of anesthesia was 4 h (range 1.5–10.2 h). Forty-six of the children were anesthetized with a volatile agent-based technique; 53 with a opioid-based technique; and 9 with a combined regional-general technique. No problems with airway management were encountered in those patients with mediastinal tumors.

Intraoperative hypertension and tachycardia accompanying tumor manipulation were extremely uncommon in the study population (<3%). In addition to the child described above, these changes occurred in only two other children, both of whom had elevated baseline catecholamine levels. One was a 10-mo-old boy with stage III neuroblastoma who presented with a history of excessive diaphoresis, progressive weakness in the lower extremities, and bowel and bladder dysfunction.

During emergency laminectomy for decompression, tumor manipulation was associated with an increase of HR from 135 to 180 bpm, an increase of BP from 90/60 to 135/90 mm Hg, and an increase of rectal temperature from 35.5 to 38.8°C. During a repeat laminectomy 2 mo later, an intraoperative elevation of serum epinephrine was documented. The other child was a 3.5-yr-old girl who presented with hip pain and was found to have stage IV neuroblastoma. After chemotherapy, she underwent adrenalectomy, during which tumor manipulation was accompanied by a 40%–50% increase in both HR and BP that was treated with propanolol.

Whereas combined tachycardia and hypertension during tumor manipulation was uncommon, other intraoperative vital sign changes did occur in our review population. Twenty-nine percent of the children had a significant increase in HR during tumor dissection without change in BP or temperature. Forty-five percent of the children had a significant decrease in systolic BP after tumor excision. In most of these cases, BP was restored with infusions of blood and/or crystalloid; no patient required vasopressor therapy. No intraoperative dysrhythmias were noted in any patient, including the 71 patients who received halothane.

Our review population included the full range of clinical stages and pathologic variations of neuroblastoma. Final clinical staging of the tumors demonstrated that 35% were stage IV, 5% were stage IVS, and the rest were evenly distributed among stages I–III. Final pathologic characterization of the tumors demonstrated that 70% were neuroblastoma, 23% ganglioneuroblastoma, and 6% ganglioneuroma. The distribution of clinical stages and pathologic types was similar for the nine symptomatic patients as for the population at large, and, as noted above, all three children with intraoperative hypertension had neuroblastoma (stages II–IV).

Discussion

Neuroblastoma is the most common solid tumor of infancy and the third most common malignancy of childhood (15). Along with the related tumors ganglioneuroblastoma and ganglioneuroma, neuroblastoma is an embryonal tumor of neural crest origin that may arise at any site in the sympathetic nervous system, especially the paravertebral sympathetic ganglia, adrenal medulla, and preaortic retroperitoneal paraganglia. Metastases are present in more than half the cases at the time of diagnosis, particularly in bone cortex, bone marrow, and lymph nodes. The tumor is staged (I–IV) according to degree of local extension and metastasis, stage IVS specifying remote disease in liver, skin, and/or bone marrow. As shown by our study population, the clinical presentation is extremely varied and is often directly related to the site of origin of the tumor. The clinical diagnosis of neuroblastoma is confirmed by radiologic and chemical studies, including urine and/or serum catecholamines (norepinephrine, epinephrine, dopamine) and their metabolites (vanillylmandelic acid and homovanillic acid); some elevation of catecholamines is found in 80%–90% of patients (15,16). Primary surgical resection of neuroblastoma is reserved for stages I and II; for the more advanced stages, treatment may entail chemotherapy, radiation therapy, and even bone marrow transplantation (17).

The release of catecholamines by neuroblastoma tumors may produce fever, diaphoresis, flushing, diarrhea, and hypertension. The latter sign has been reported in as many as 35% of cases (15,18). In our review population of 108 patients, only 9 children had signs or symptoms suggestive of catecholamine release, including 2 children with a history of well-documented hypertension. Fifteen additional children had mild elevation of blood pressure on admission without other related signs or symptoms.

Our study suggests that the incidence of clinically important cardiovascular signs indicative of catecholamine release during tumor resection is <3%. Although tachycardia and hypertension may accompany surgical manipulation of any tumor in the chest or abdomen, the association of acute vital sign changes with the marked increase in serum norepinephrine concentration in our reported patient strongly indicates that these are indeed catecholamine-related changes. In contrast to patients with neuroblastoma, virtually all patients with pheochromocytoma demonstrate intraoperative hypertension if α-adrenergic blocking drugs are not given before surgery (19). However, as demonstrated by our case report, patients with neuroblastoma may mimic those with pheochromocytoma, and clinically adequate preoperative treatment with α-adrenergic blocking therapy may not preclude intraoperative hypertension.

The relative infrequency of clinical evidence of catecholamine excess in patients with neuroblastoma resection compared to those with pheochromocytoma may be due to a variety of factors. Neuroblastoma tissue may lack the enzyme that *N*-methylates norepinephrine to produce epinephrine (20). The tumor may also have a variable mixture of both adrenergic and cholingeric cells (21) and a variable concentration of the enzyme responsible for the conversion of dopamine to norepinephrine (β-hydroxylase) (16). Finally, neuroblastoma tissue often has a paucity of intracellular storage granules in which synthesized catecholamines are stored (22–24). Quantitative analysis of the neurosecretory granules in a tumor may be, in fact, difficult as the density of these may vary greatly within areas of a given tumor and between different microscopic fields. When a large number of secretory granules in the cells of neuroblastoma tissue are present, a clinical response during tumor resection similar to that of pheochromocytoma can be seen (25). All three of the children with intraoperative hypertension in our study population had tumors that were rich in neurosecretory granules.

Apparent also from this review is the high proportion of patients who had clinically important episodes of hypotension after removal of neuroblastoma tumor (45%). Although hypotension due to blood loss and caval compression during tumor excision from the chest or abdomen would be anticipated, this high incidence of hypotension after tumor excision is noteworthy. In all cases, BP was restored with adjustments of anesthetic management, with infusion of fluids, and without vasopressor therapy. Previous experience with the anesthetic management of patients with pheochromocytoma supports the use of volume repletion rather than vasopressor therapy in the treatment of hypotension after tumor resection (19). Possible explanations for the commonly observed hypotension after tumor removal in this series of patients with neuroblastoma include a contraction of intravascular volume due to surgical fluid losses, excess of anesthetic depth during surgical closure, or vasodilation associated with a decrease in catecholamine levels.

Our findings have implications concerning the anesthetic management of patients undergoing resection of neuroblastoma. For the vast majority of these patients, signs of intraoperative catecholamine excess are not encountered, although the need to restore intravascular volume after tumor resection can be anticipated. Patients who have marked hypertension and other preoperative signs and symptoms of catecholamine excess may develop intraoperative problems typical of patients with pheochromocytoma. These patients, like those with pheochromocytoma, should undergo preoperative intravascular volume repletion and control of hypertension with α-adrenergic blocking agents until clinical signs and symptoms are controlled (7,19). Once α-adrenergic block is established, β-adrenergic block may be instituted to control secondary tachycardia and tachydysrhythmias. Preoperative treatment with adrenergic blocking agents should blunt, if not ablate, cardiovascular responses to surgical stress and tumor manipulation. Intraoperative hypertensive episodes that do occur can be managed with sodium nitroprusside or with a short-acting α-adrenergic blocking agent such as phentolamine.

There is no evidence from this study or other reports to support the use of one anesthetic agent or technique over others. Successful intraoperative management of patients with pheochromocytoma has been reported using all the volatile agents and opioids (5,6,19). Our experience here confirms the safety of these agents, as well as the safety of a combined regional-general anesthetic technique, in the management of patients with neuroblastoma. In patients with a clinical picture similar to that of the infant described here, it may be prudent to anticipate the potential adverse effects of exogenous epinephrine and to avoid epinephrine-containing local anesthetic agents. Finally, although mediastinal neuroblastomas are generally located in the posterior compartment and do not pose significant problems for airway management, it is important to recognize possible consequences of any tumor that compresses the airway (26,27) as well as the ability of this specific tumor to cause significant compromise to the airway (28).

In conclusion, we report a case of neuroblastoma resection that was associated with intraoperative hypertension despite preoperative treatment with an α-adrenergic blocking agent. The review of our anesthetic experience with neuroblastoma over the past 20 yr indicates that the actual incidence of intraoperative hypertension associated with tumor manipulation is <3%. By contrast, hypotension that follows tumor resection is a common occurrence during the anesthestic management of neuroblastoma.

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Letters to the Editor

Propofol in Cardiac Catheterization

To the Editor:

We read with interest the article by Lebovic et al. (1) on the comparison of propofol versus ketamine for anesthesia in pediatric patients undergoing cardiac catheterization. We agree that propofol may well be an alternative to ketamine, but we must reemphasize the cautionary note sounded by the authors—propofol is a myocardial depressant (2,3), and it should be used with this side effect borne in mind.

Although mentioned in their article, Lebovic et al. (1) did not emphasize that their method of inducing anesthesia with propofol differs substantially from that commonly used in adults or children (4,5). Usually, a dose of 2–2.5 mg/kg of propofol is used and administered over a total of 40–60 s. Lebovic et al. (1) used 0.5-mg/kg increments, a relatively small dose, with each increment administered over 60 s. The hemodynamic effects of this method of administration may differ substantially from when the usual dose is administered more rapidly, as is usually the case. Another point that we feel must be stressed is patient selection: until more data are available, it is probably not only prudent but logical to avoid propofol in critically ill pediatric patients presenting for cardiac catheterization. Larger doses will contribute to alterations in cardiac output, with reversal of shunt flow causing much more significant alterations in cardiorespiratory variables than those described by Lebovic et al. (1).

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To the Editor:

We read with interest the clinical research report by Lebovic et al. (1) on the usage of propofol as an anesthetic in pediatric patients presenting for cardiac catheterization. The authors indicated that this was the first presentation to describe the use of propofol in pediatric congenital cardiac diseases and further concluded that "propofol anesthesia is a practical alternative for pediatric patients undergoing elective cardiac catheterization and may be preferable to ketamine because of the significantly shorter recovery time." This recommendation must be qualified before wide application. We would like to address the following two points.

First, congenital heart disease is not a single disease but a vast array of anatomic anomalies. Each anomaly is associated with a set of distinctive clinical features. The clinical course and the physiologic responses to different pharmacologic interventions, as well as the homeostatic reflex to various stimuli during the administration of anesthetics, can be extremely diverse. Propofol is known to cause myocardial depression. In the investigation described by Lebovic et al. (1), it was discovered that 7 of 10 patients developed decreased mean arterial pressure after they were given a propofol infusion. In certain congenital heart diseases (e.g., aortic stenosis), a pharmacologically induced decrease in arterial blood pressure can precipitate adverse patient outcome (2). The use of propofol in patients with aortic stenosis must therefore be considered contraindicated. The notion that one anesthetic can be prescribed for a group of diverse cardiac diseases seems imprudent.

Second, the demographic data of the patients enrolled in the study mostly matched when age, body weight, arterial blood oxygen saturation range, and duration of catheterization were compared in the two groups (propofol and ketamine). However, the most important clinical feature in patients undergoing cardiac catheterization is not age, body weight, arterial oxygen saturation, or duration of catheterization, but diagnosis. The diagnosis of congenital cardiac defect, unfortunately, did not match in the two groups. For example, three patients in the ketamine group, but none in the propofol group, were diagnosed as having truncus arteriosus. (The number of patients in the study, 10 in each group, is too small for meaningful statistical analysis among the different diagnoses.)

In conclusion, we strongly believe that there is no single anesthetic that is ideal for providing sedation for cardiac catheterization. The result of the comparison between propofol and ketamine is probably not valid, because clinical diagnoses between the two groups of patients did not match.

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In Response:

The cautionary note sounded by Drs. Lippmann and Ginsburg is appropriate. We would add, however, that only a small fraction of pediatric cardiac catheterization patients would be expected to experience arterial desaturation or hemodynamic decompensation in response to propofol. Obviously, the principle of slowly administering lower doses of depressant anesthetics applies to all patients with cardiac disease, especially those with right-to-left shunting.

Drs. Kao and Norton are correct in pointing out that congenital heart disease represents a wide spectrum of anatomic and physiologic abnormalities and that patients with certain lesions may respond adversely to propofol anesthesia. This point was also emphasized in the discussion section of our article and is a point that is well understood by the readership of this journal. However, we disagree with their contention that the presence of three patients with truncus arteriosus in the ketamine group invalidates the results of the study. They could just as easily have argued that there was only one patient with a double-outlet right ventricle in the propofol group. A study of several hundred patients would be necessary to achieve "statistical" equity between the groups. It is not necessary or economical to proceed with such a massive study to prove what is obvious from our limited study. The point of the study is not that propofol should be used in all patients with congenital heart disease; rather, in properly selected patients, it is a satisfactory anesthetic agent with markedly improved recovery characteristics.

In reviewing our further experience with propofol in the cardiac catheterization laboratory, it is being used as the primary anesthetic agent in approximately 70% of cases. We currently induce anesthesia using 1-mg/kg bolus doses of propofol, which is repeated once if necessary. Our initial infusion rate is 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$, which is titrated upward or downward as necessary. Anesthesiologists, as well as pediatric cardiologists and postanesthesia care unit staff, are pleased with the recovery characteristics of propofol. It is likely that propofol will be used more commonly in the future, given the current emphasis on ambulatory care.

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Propofol for Radiation Therapy in Small Children

To the Editor:

We agree with Martin et al. (1) that propofol is an excellent anesthetic for small children with indwelling central lines undergoing radiation therapy. However, we have found that when propofol is titrated by small bolus doses or continuous infusion, children are able to maintain their natural airway in both the supine and prone positions, and repeated endotracheal intubation can be avoided. A retrospective chart review of a 1-yr period showed that we had used intravenous anesthesia for 153 of the 156 high-voltage radiation therapy procedures for which anesthesia was requested. Propofol was used as the sole anesthetic in 72 cases and in combination with other anesthetics (midazolam, ketamine, droperidol) in 62 cases. In none of these 153 procedures was the trachea intubated. The radiation procedure itself is painless, and only light levels of anesthesia are needed to keep the child motionless. Patients were monitored with a pulse oximeter, electrocardiograph, respiratory inductane monitor, and an automated oscillometer for automatic arterial blood pressure measurement. Monitors were visible through a window in the treatment room. The children were observed indirectly via videocamera when the anesthesiologist left the room for the 3–7 min required for the treatment. Intravenous anesthesia without endotracheal intubation eliminates the need for an anesthesia machine and waste gas scavenging in a remote location and eliminates the risk of laryngeal trauma from repeated instrumentation. Propofol can be titrated to achieve adequate sedation without undue respiratory or cardiovascular depression. When propofol is used alone, recovery is rapid, and patients are alert before transport. Those patients undergoing daily treatments were able to continue normal daily activities and maintain nutrition. As with all potent anesthetics, careful observation and monitoring of the patient are required, and appropriate equipment and supplies must be available for the management of adverse drug effects or reactions.

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1. Martin LD, Pasternak LR, Pudimat MA. Total intravenous anesthesia with propofol in pediatric patients outside the operating room. Anesth Analg 1992;74:609–12.

In Response:

We appreciate the interest that Drs. Setlock and Palmisano have shown in our case report with regard to the use of propofol in pediatric patients outside the operating room (1). We agree with them that propofol is an excellent anesthetic for small children undergoing procedures remote from the operating room and that it has several distinct advantages over previously utilized techniques. We also recognize that airway management for these cases is somewhat a matter of preference. However, this decision must be made in the context of the individual institution. As stated in our article, we chose to carefully intubate the tracheas of our patients for several reasons: (a) one patient had to be transported to several different locations for multiple radiologic procedures; (b) our radiologic suites are very distant from the operating room should assistance be required; and (c) the patients had to be placed in multiple positions (supine, prone, and lateral). We had no evidence of airway trauma from repeated airway instrumentation when appropriate care was taken. As stated in the article, more experience with this anesthetic technique may demonstrate that oral intubation may not always be necessary. As Drs. Setlock and Palmisano have demonstrated, we also have found that in selected cases, carefully titrated infusions of propofol achieve adequate levels of sedation for these painless procedures and that patients are able to maintain their natural airways. However, each and every procedure must be planned with the particular institution's personnel, facilities, and limitations in mind. We therefore believe that the method of airway management must be left to the individual anesthesiologist, who clearly has an understanding of the local environment in which he or she is working.

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1. Martin LD, Pasternak LR, Pudimat MA. Total intravenous anesthesia with propofol in pediatric patients outside the operating room. Anesth Analg 1992;74:609–12.

Myelopathy and Back Pain —Take Heed

To the Editor:

Two articles in sequential issues of *Anesthesia & Analgesia* should have alerted anesthesiologists to the fact that local anesthetics are not innocuous drugs (1,2). However, these articles did not address other issues that anesthesiologists also should be aware of.

Rigler et al. (1) state that "Despite its long history, clear guidelines for safe administration of local anesthetics via an indwelling catheter remain to be established." A review of the most recent textbooks confirms this statement (two contained nothing on the subject and five only a paragraph) (3–9). Evidently, these books reflect the clinical situation, namely, that intermittent-injection spinal anesthesia has been little used or taught during the past 20 yr. Nevertheless, since 1940, both tetracaine and procaine have been used safely in intermittent-injection spinal anesthesia (10–16). However, tetracaine was not administered as in the one case cited by Rigler et al. (1). Futhermore, 5% lidocaine in 7.5% glucose or dextrose, which was used in the other three cases cited by Rigler et al. (1), is intended for use in the single-injection technique. Package inserts for this preparation of lidocaine state that "If the technique is properly performed and the needle is properly placed in the subarachnoid space, it shouldn't be necessary to administer more than one ampule (100 mg)" (17). It contains no statement about plastic tubing (catheter). Finally, one wonders why for spinal anesthesia, intermittent-injection rather than single-injection techniques were used. Compared with the single-injection technique, intermittent injection is fraught with more complications. All four cases cited by Rigler et al. (1) required only a sensory dermatome level to the tenth thoracic dermatome and durations of 1, 2.5, 3, and 3.5 h. A single injection of no more than 10 mg of hyperbaric tetracaine with duration extended by the addition of 0.2 mg of epinephrine (4–5 h) or 5 mg of phenylephrine (5–7 h) would have sufficed.

Hynson et al. (2) suspected "local irritation of the muscles and soft tissues" from chloroprocaine. When chloroprocaine was reintroduced for epidural block in 1971, it contained sodium bisulfite, a known tissue irritant (18,19); however, myelopathy from it did not surface until 1980 (20). In 1988, the bisulfite in chloroprocaine was replaced with the chelating (stabilizing) agent disodium ethylenediaminetetraacetate (EDTA) (21). After injection of this stabilizer into the subarachnoid space of rabbits, it was concluded that the investigation ". . . suggested EDTA has neural blocking effects and may cause complications" (22). One wonders what would happen if 20 mL or more was injected unintentionally into the subarachnoid space of patients? Perhaps nothing, but then, time will tell. Nine years (1971–1980) elapsed before myelopathy from chloroprocaine containing sodium bisulfite surfaced.

Hopefully, these two articles (1,2) have notified physicians that trespassing clinically with local anesthetics that have not been carefully and thoroughly researched for the techniques for which they are to be used, can result in significant complications.

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In Response:

We appreciate Dr. Moore's comments. As we have previously stated (1), the purpose of our article was to alert clinicians to a potential risk, to suggest an etiology for the four cases of cauda equina syndrome, and to begin to establish guidelines for the safe administration of local anesthetic through an indwelling subarachnoid catheter (2).

Dr. Moore agrees that clear guidelines for continuous spinal anesthesia (CSA) do not exist. Nonetheless, he suggests that since 1940, tetracaine and procaine have been used safely for intermittent-injection spinal anesthesia. However, his citation of the literature is incomplete. For example, the cited report by Schuhmacher and Eversole (3) provides only a description of the technique used for CSA at the Lahey Clinic during the late 1930s and early 1940s; it does not report results nor review complications. The citations do not include the subsequent report published 4 yr later by Nicholson and Eversole (4) that did review the Lahey Clinic experience during that same period and documented five cases of neurologic complications among 21,000 tetracaine spinals. Of these five cases, three occurred with a continuous spinal technique, two of which were classified as cauda equina syndrome. (Unfortunately, the report does not indicate the relative number of cases performed with a single-injection or a continuous technique.) Dr. Moore's references also do not include other reports in which neural injury was associated with CSA performed with procaine or tetracaine (5,6). Furthermore, the relationship between injury and anesthetic agent may not always be appreciated—as we noted in our article, the three cases of severe urinary retention described in Apgar's (6) series of 422 cases of CSA performed with procaine likely reflect local anesthetic neurotoxicity. Thus, the use of tetracaine or procaine for CSA as described by these early investigators cannot be viewed as entirely safe.

In the four cases of cauda equina syndrome reported in our article (2), there was evidence of a focal sensory block, and to achieve adequate anesthesia, a dose of local anesthetic was administered that was greater than that usually used with a single-injection technique. We postulated that the combination of maldistribution and a relatively high dose of local anesthetic exposed neural tissue to a toxic concentration of anesthetic. We have been able to demonstrate in a model of the subarachnoid space that when maldistribution occurs, the concentrations achieved with repeated administration of hyperbaric local anesthetic are potentially neurotoxic (7).

However, prior to our report of the four cases, concerns with regard to neurotoxicity from high doses of local anesthetic were confined primarily to chloroprocaine (8). The dosages of local anesthetics commonly administered intrathecally have been tailored to achieve an appropriate dermatomal level and duration, not to avoid neurotoxicity. Previous reports of CSA often have commented on the wide variability in anesthetic requirement and suggested, as in the Lemmon (9) article cited by Dr. Moore, that the "dose should be given as needed." Although the package insert for 5% lidocaine indeed does suggest that 100 mg should be sufficient, it fails to state that this dose should not be exceeded nor caution that neural injury might result. Conversely, higher doses of lidocaine have often been recommended or administered. For example, the textbook by Lund (10), which Dr. Moore cites, suggests a dose of "100 to 150 (or more) mg for upper abdominal procedures," whereas Mörch et al. (11), using a catheter technique, administered doses of 150 to 550 mg, with doses as high as 250 mg administered to establish the initial block.

Dr. Moore believes that 5% lidocaine in 7.5% dextrose is for use in a single-injection technique, noting that the package insert does not mention administration of the anesthetic through a catheter. This view is inconsistent with his belief that tetracaine and procaine are appropriate for CSA, because neither the insert for procaine (12) nor for tetracaine (13) refers to such use. It is also inconsistent that Dr. Moore cites Lund (10) but fails to acknowledge Lund's conclusion that "Any local anesthetic agent which is suitable for [single-injection] spinal anesthesia may be used for [CSA]." Of note, Mörch et al. (11), one of the first to report 5% lidocaine in 7.5% dextrose to be "a safe, potent and satisfactory agent for spinal anesthesia," delivered the anesthetic through a catheter. However, a major point in our article was that neurotoxic injury resulted from the combination of maldistribution and a high dose of relatively concentrated local anesthetic. Consequently, we suggested that the lowest effective concentration of local anesthetic be used. This recommendation is based on data indicating that the risk of neurologic injury is, at least in part, concentration dependent (14). If maldistribution occurs, the concentration of local anesthetic will not be adequately diluted by cerebrospinal fluid. Therefore, we recommend that 5% lidocaine not be used—this concentration is in excess of that needed for adequate blockade. We suggest that lower concentrations be selected for single-injection spinal anesthesia as well: the appropriateness of injecting a particular local anesthetic into the subarachnoid space should not be based on whether it is to be administered through a needle or a catheter, nor with a single-injection or a continuous technique, but, rather, the intrinsic characteristics of the anesthetic solution.

We also recommended that a test dose should be administered, after which the extent of blockade should be assessed; if maldistribution of anesthetic is suspected, maneuvers such as changing patient position, altering the lumbosacral curvature, switching to a different baricity of local anesthetic, or manipulating catheter position should be used; if these maneuvers fail to correct the problem, the technique should be abandoned. We have suggested that similar cautions be applied when repeating single-injection spinals that have failed to provide adequate analgesia (15). Maldistribution *can occur* with a single-injection technique, and there is the potential (albeit less than with an indwelling catheter) for repeat injections to distribute in the same restricted pattern; this restricted distribution could result in neurotoxic concentrations of local anesthetic—a review of the closed-claim database appears to support these concerns (15).

We do not agree with Dr. Moore that, in comparison with a single-injection technique, CSA is fraught with complications. Conversely, the continuous technique offers potential advantages. With CSA, the duration of anesthesia can be controlled by administering incremental doses of short-acting local anesthetics, and there is evidence to suggest that anesthesia can be maintained for extended periods without prolonging recovery. In a preliminary study, we observed that the length of stay in the postanesthesia care unit was unrelated to the duration of the surgical procedure (16). Although the single-injection technique also can provide anesthesia for extended periods (e.g., addition of a vasoconstrictor to tetracaine), the inability to predict anesthetic duration or surgical time accurately can lead to failure of the spinal technique or to prolonged recovery. In addition, CSA allows greater control of the extent of blockade, which, in a preliminary study, has been shown to correlate with hypotension, bradycardia, and nausea and vomiting (17); additional preliminary data suggest that patients receiving a continuous technique have a lower requirement for vasopressors (18).

We appreciate and share Dr. Moore's concern that the renaissance in regional anesthesia flourish; and we do hope, as Dr. Moore suggested, that our article will serve to alert clinicians that "local anesthetics are not innocuous drugs."

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Epidural Hematoma: Was Catheter Removed During Complete Anticoagulation?

To the Editor:

A recent case report linked the occurrence of an epidural hematoma to the presence of a congenital spinal arteriovenous abnormality (1). However, review of the case presentation raises a basic question—did removal of the epidural catheter while the patient was still undergoing anticoagulation therapy result in the epidural hematoma?

A 71-yr-old man underwent a carotid endarterectomy under cervical epidural anesthesia. Heparin (5000 U) was administered intravenously. The epidural catheter was removed at the end of the procedure, approximately 120 min after the dose of heparin, without checking coagulation studies. Approximately 30 min later, the patient began complaining of discomfort in the chest, arm, and back. Emergent surgical exploration revealed a cervical epidural hematoma and an "extensive plexus" of veins covering the dura. Coagulation studies were performed approximately 260 min after the heparin dose and were normal.

Other cases have been reported in which an epidural catheter was removed from a patient undergoing anticoagulation therapy, who went on to develop an epidural hematoma (2–4). In one case, heparin (5000 U) was administered 70 min before the epidural catheter was removed. At 2 h, a Lee-White clotting time remained elevated (21 min; normal 5–15 min) (3).

Recommendations exist with regard to the removal as well as the insertion of epidural catheters. One group recommended "frequent activated clotting time analyses" to ensure neutralization of heparin activity before epidural catheter removal (5). An editorial published in the newsletter of the American Society of Regional Anesthesia stated that one should "leave the epidural catheter in place until all systemic anticoagulation is neutralized or reversed" (6).

Therefore, the presence of a congenital spinal arteriovenous abnormality may predispose a patient to an epidural hematoma; but the removal of an epidural catheter when a patient remains in an anticoagulated state will do so as well. An epidural catheter should be left in place until anticoagulation has been corrected. Removal can then be accomplished safely.

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In Response:

Dr. Stevens asks a fair question: "was the epidural catheter removed during complete anticoagulation?" There were no clinical signs of excess bleeding or delayed clot formation during the carotid endarterectomy. Blood samples that were obtained at the onset of symptoms did clot. The hematologist found no clotting defects. It remains that this does not rule out continuing anticoagulation activity. The wormlike nest of veins in the epidural space at surgery associated with the hemangioma on the chest wall still remains a possible cause for the hematoma and the reason for the original report. I agree that the coagulation status must be established before removal of the epidural catheter.

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Long-Distance Anesthesia

To the Editor:

I should like to agree with Dr. Boyd and coworkers (1) concerning "long-distance anesthesia," which I also use in ophthalmic anesthesia. There may, however, be a problem with standard calculated minute volume (Vmin) and tidal volume (Vt).

The anesthetic dead space is from the Y-piece to the tip of the endotracheal tube. There is, however, further effective dead space. This further dead space is in the compliance of the ventilatory tubing. Most tubing in use has a compliance of 3–5 mL/cm H_2O at room temperature (20°C); therefore, with an airway pressure of 20 cm H_2O, there is 60–100 mL of fresh gas used in the expansion of the tubing. If the tubing is doubled in length, then the expansion volume rises to 120–200 mL.

The Vt measured at the inspiratory or expiratory port of the ventilator will be patient tidal volume plus expansion volume. When measured at the Y-piece, only patient tidal volume is measured. It is possible to measure Vt at the Y-piece by an electronic spirometer or, more easily, by an in-line vane-type or resistance flowmeter.

It is therefore important in long-distance anesthesia to either know the compliance of the tubing used or to measure Vt at the Y-piece. Alternatively, end-tidal CO_2 measured at the Y-piece also confirms adequate alveolar ventilation despite the length of the tubing.

For ophthalmic anesthesia, I have been using a closed-circuit anesthesia system with ventilatory tubing 2 m in length (4 m overall). This allows full access to the patient's head for surgical purposes. Knowing the compliance of the tubing, I can calculate the actual tidal volume that the patient is receiving. I confirm adequate alveolar ventilation by monitoring end-tidal CO_2 and hemoglobin O_2 saturation.

I would agree with Dr. Boyd and coworkers that there appears to be a perception that the patient must be close to the ventilator. However, assuming that all of the above are taken into account, then there is no reason why the ventilator cannot be a reasonable distance from the patient, yet still be in a safe location and provide surgical access.

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In Response:

We were encouraged by Dr. Dunphy's letter with regard to our article on long-distance anesthesia, which he also utilizes.

We certainly concur with his statements about the compliance of the ventilator tubing as a factor in calculating the delivered tidal volume. To compensate, we usually add approximately 100 mL to the estimated tidal volume required by the patient. The volume is then adjusted for an end-tidal CO_2 of 35 mm Hg. Furthermore, the hemoglobin O_2 saturation is monitored in every patient.

This was an omission on our part, and we appreciate Dr. Dunphy's comments.

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An Atraumatic Oral and Nasotracheal Intubation Guide Probe

To the Editor:

I would like to comment on the case report by Knuth and Richards (1). Tracheal intubation via the nasal approach is not a rare event. In children, nasal intubation is used for amygdalectomy or to adequately fix the endotracheal tube when the child's head is too far from the anesthesiologist. In adult surgery, nasal intubation is performed in otolaryngology—head and neck surgery and in oral and dental surgery.

In our university clinic, we always use a tube with a flexible guide probe and a blunt extremity for all oral or nasal endotracheal intubation (Figure 1). This probe, which is well adapted to the endotracheal tube diameter, has two advantages: (a) it facilitates oral intubation without larynx trauma when laryngoscopy is difficult, and it can be used together with the Magill forceps to facilitate intubation; (b) it prevents the inhalation of foreign bodies and keeps anatomic structures (adenoids or turbinate) out of the airway. This probe also prevents insufflation in the airway of an object set in the endotracheal tube. The tube is easy to use and without risk for the patient because the probe is always plastic, and its extremity is blunt. The close fit of the probe and the endotracheal tube is important, because it prevents a foreign body from coming between the probe and the endotracheal tube.

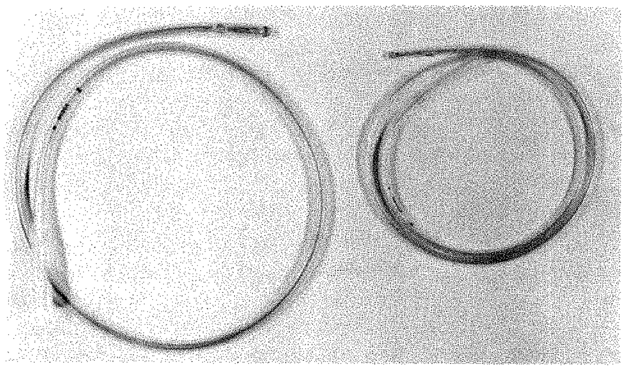

Figure 1. Esophageal tubes (5, 6, and 8 mm) manufactured by Rüsh AG, Kernum, Germany.

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More on Epidural Fentanyl Analgesia

To the Editor:

In their discussion of epidural fentanyl analgesia, Glass et al. (1) comment as follows: "Using the epidural route, the concentration and volume of the fentanyl dose as well as the site of the epidural catheter in relation to the site of surgery is important in providing optimal analgesia with the smallest dose." I suggest that volume and concentration are not important. I do believe that epidural placement site is important in providing superior analgesia with smaller doses of fentanyl and wonder why, considering the above statement, Glass et al. decided to place catheters in the low lumbar epidural space. It would have been more appropriate to place the catheters in a low thoracic interspace, because the opiate receptors are found in the spinal cord, which ends at L-2.

As residents, anesthesiologists learn epidural therapy using bolus doses of local anesthetic for anesthesia. Now we are using continuous infusions of narcotics for epidural analgesia. One cannot consider these to be equivalent in theory or practice. I believe that a slow, continuous infusion, for example, either 3 mL/h (0.05 mL/min) or 6 mL/h (0.1 mL/min) to administer 60 μg/h of fentanyl, presents an inconsequential difference of volume to structures in the dynamic epidural space. The argument is that dose is important and concentration (volume) less critical. The finding of an optimal concentration for bolus epidural fentanyl by Welchew (2) does not necessarily apply to a continuous fentanyl infusion.

Glass et al. (1) claim that intravenous and epidural fentanyl provide equivalent analgesia when administered by patient control. In their study, catheters were placed in the lumbar epidural space. The epidural space has a large potential volume in the lumbar region compared with the thoracic region. With narcotics administered in the lumbar epidural space, which is dynamic and filled with adipose tissue and blood vessels, one would assume that very little if any of the analgesic effect would be neuraxial. The obvious reason is that the epidural structures would distribute lipophilic opioids systemically. Thus, I agree with Glass et al. (1) that intravenous fentanyl is probably equivalent to lumbar epidural fentanyl. Perhaps morphine, which is hydrophilic, is the only opioid appropriate for analgesia with lumbar catheter placement.

Nonetheless, I use fentanyl as my drug of choice for epidural analgesia, with catheter placement determined by the dermatomal origin of pain. There is support for this technique by at least one clinical study. In an abstract by Bodily et al. (3), it is reported that fentanyl epidural analgesia for postthoracotomy pain is influenced by the site of epidural catheter placement. Those patients who had lumbar catheters were not as comfortable as those who had thoracic catheters, even though they received 50% more fentanyl. I draw two conclusions: (a) epidural fentanyl provides segmental analgesia; and (b) there is a significant neuraxial component of analgesia with thoracic epidural administration of fentanyl. The Glass et al. (1) research might have confirmed the Bodily et al. (3) study had they placed their catheters appropriately.

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To the Editor:

Glass et al. (1) presented an interesting approach to postoperative pain management with the use of patient-controlled administration of fentanyl via the epidural and intravenous routes. However, we believe that their conclusion, that analgesic effects of fentanyl in the epidural space are due to plasma concentrations, is somewhat misleading. In view of the site of infusion, one should not be surprised that the analgesic effect of fentanyl is due primarily to systemic rather than neuraxial antinociceptic activity. An alternative conclusion that one may draw from this study is that for a drug such as fentanyl to be effective, one must place it close to its dermatomal site of desired action.

In support of this, and in contrast to Glass et al. (1), we find epidural fentanyl infusions to be very effective in low doses (i.e., 1.0 $\mu g \cdot kg^{-1} \cdot h^{-1}$) in the control of postoperative pain in patients with upper abdominal and flank incisions. Pharmacokinetic work by Gourlay et al. (2) very clearly defined the potential limitations when using epidural fentanyl for postoperative pain control. Infusions via an L3-4 catheter demonstrated that fentanyl, being very lipophilic, would not diffuse well in a cephalad direction. As a consequence, to achieve good pain control with epidural fentanyl, one must place it at the appropriate dermatomal level, as Wolfe et al. (3) did and as we do.

Opioid activity in the spinal cord is primarily the result of nociceptive inhibition at the dorsal horn level of entry (i.e., for an upper abdominal incision at the T8-10 dermatomal level). One must place a catheter at that level to expect a good result when using highly lipophilic opioids, such as fentanyl, sufentanil, or alfentanil. Our experience with over 600 epidural infusions demonstrates that low-dose fentanyl/bupivacaine infusions (5 μg/mL and 0.125%, respectively) at rates of 6–12 mL/h give excellent relief for postoperative pain.

Patient satisfaction with our continuous infusion technique is very high, especially at night. This technique does not require that patients awaken in pain before giving themselves a dose of analgesic, as would patient-controlled analgesia. In theory, continuous epidural infusions may permit the use of lower doses of narcotics, in part due to the maintenance of steady-state drug concentrations at the dorsal horn. However, patient comfort is the primary goal, not necessarily saving doses of narcotic drugs.

In conclusion, we have found epidural infusions to be both highly effective for control of postoperative pain as well as very safe for use on general surgical wards. We offer this as a respectable alternative to the use of epidural patient-controlled analgesia.

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In Response:

Drs. Nicholson and Rowlingson and Dr. Hubbard all raise a very important issue with regard to positioning the epidural catheter when administering epidural fentanyl. It is true that the same principles pertaining to the administration of epidural local anesthetics cannot be extrapolated to the administration of epidural opioids. Local anesthetics act on nerve roots as they pass through the epidural space, whereas opioids have to traverse the dura and cerebrospinal fluid to reach the dorsal horn of the spinal cord to reach their site of action. Because the spinal cord ends at L-1 in the adult, a lumbar epidural catheter at or below this level will increase the distance that the opioid has to traverse, compared with a catheter placed at the thoracic level. The implication is therefore that using an epidural catheter placed at the lumbar level would require a larger dose of fentanyl to provide effective analgesia than an epidural catheter placed over the involved dermatome at the thoracic level. This supposition has not been systematically investigated. A recent study did compare lumbar with thoracic epidural administration of fentanyl after thoracic surgery (1). The investigators were unable to show a significant difference between the two routes of administration in either quality of analgesia, dose, or fentanyl plasma concentrations. It is also interesting to note that Drs. Nicholson and Rowlingson recommend an infusion of 30–60 μg/h of fentanyl (in combination with 0.125% bupivacaine). This hourly dose of fentanyl is the same as that (40–50 μg/h) required intravenously by the patients in our study (2) (as well as others [3]) to achieve very satisfactory analgesia. It should also be noted that the less lipid-soluble opioids will tend to migrate cephalad in the cerebrospinal fluid. Therefore when an opioid (especially one like morphine) is administered in the lumbar epidural space, the onset of analgesia may be altered but not the efficacy of the dose.

It is common for a physician to insert a lumbar epidural catheter for the administration of local anesthetics intraoperatively and then utilize this same catheter for postoperative pain management. Thus, the results of our study are pertinent for normal clinical practice and enable the clinician in such instances to make a more rational choice as to either the drug (fentanyl vs morphine) or mode of its administration (epidural vs intravenous) that is optimal for patient postoperative pain management.

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Malignant Hyperthermia During Sevoflurane Anesthesia

To the Editor:

We read with interest the article by Ochiai and colleagues (1) describing the possible association between the administration of sevoflurane and the development of malignant hyperthermia (MH). Because of the important implications of such findings, we believe that a critical examination of their case reports is necessary. We agree that sevoflurane may be associated with MH, as we had previously reported (2).

In the first case report by Ochiai et al. (1), the findings are consistent with the development of MH; but we also note that impairment of CO_2 absorption by sevoflurane may also cause several of the findings (e.g., increased heart rate, end-tidal CO_2). The relative contribution is difficult to discern. In the second case, we question more strongly the association between sevoflurane administration and MH. Whereas it is not certain whether the malfunction of the vaporizer suspended or overevaporated the isoflurane, the exposure to sevoflurane for only 30 min is not likely to have provoked MH. It has been shown that sevoflurane is a less potent trigger of MH than other volatile anesthetics (3). The late onset of MH by volatile anesthetics must be considered when establishing the etiology of MH (2). Also, lethal MH occurred in this patient, who had a history of general anesthesia without a previous problem. In addition, warm skin or muscle rigidity was not shown, and the ineffectiveness of dantrolene is worthy of notice. Muscle biopsy or a postmortem examination of the hypothalamus (4), or both, would have been informative.

These cases are also of interest because of the potential anesthetic interactions that may produce undesirable effects. In our institute, we have used sevoflurane frequently to induce anesthesia in children because of its rapid onset of action. Usually, isoflurane is then used for maintenance of anesthesia. The interactions between these anesthetics and others must therefore be studied, because such combinations may be used, owing to the rapid uptake and elimination of sevoflurane.

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Cannulation of Vessels Using a Spring-Loaded Device

To the Editor:

Cannulation of blood vessels is an important part of managing seriously ill patients, especially neonates and infants. The procedure requires very fine hand control and considerable practice. Although it is an operation performed many times, it can be a daunting experience for some (1).

Intravenous cannulas are designed with an introducer needle that is slightly longer and narrower than the cannula. Difficulties are usually encountered once the vessel has been punctured by the needle, and the cannula is advanced. The needle may bend considerably during insertion, making manipulation difficult (2). Additionally, the needle tip may be accidentally advanced or prematurely withdrawn, resulting in failure.

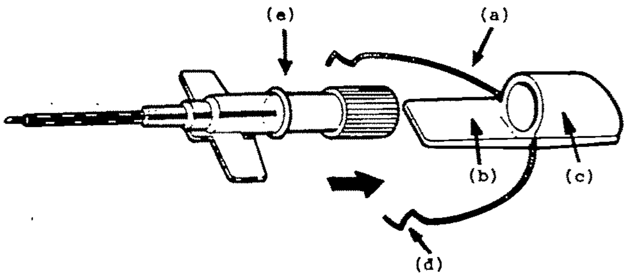

Figure 1. (a) Central venous pressure line guide wire used as spring; (b) rectangular plastic base; (c) tube to hold the hub of the cannula; (d) "Z"-shaped hook; (e) intravenous cannula with wings.

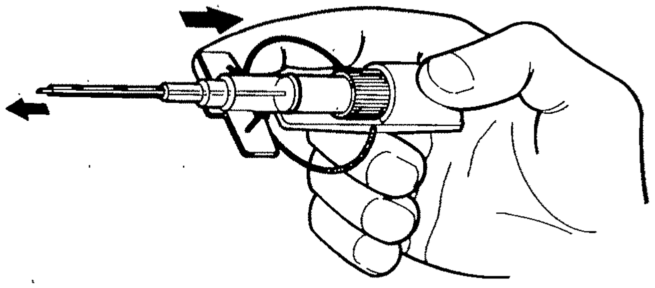

Figure 2. Cannula held with the device spring in tension.

By experiment, I have found that spring-loading the cannula greatly eases this procedure. The spring is put under tension before the vessel is punctured. Once the vessel is punctured, release of the spring pushes the cannula forward in a swift, smooth motion, avoiding the problems normally encountered.

The device (Figure 1) is constructed using a central venous pressure line guide wire that acts as a spring. While the cannula is held in place on the needle with a finger on one of the wings, the free ends of the wire are hooked over the near side of each wing (Figure 2). This puts forward pressure on the cannula. The cannula is held with the wire under tension, and the vessel is pierced as usual. Once the needle is within the lumen, signaled by a "flashback" of blood (3), the resisting finger can be released, and the cannula moves forward into the blood vessel. The spring and the needle are withdrawn, leaving the cannula in situ.

This technique was assessed in 50 infants (92% weighing <4 kg) when cannulation by the conventional method had failed. Cannulation was successful in 47 (94%) of these infants on the first attempt; only 3 (6%) required a second attempt.

By adopting this concept, a new generation of spring-loaded cannulas, long lines, and central venous pressure lines could be constructed.

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Use of Transesophageal Echocardiogram for Intracardiac Thrombus Related to Postoperative Atrial Fibrillation

To the Editor:

We describe a case in which a patient developed postoperative atrial fibrillation due to an intracardiac thrombus.

The patient was a 68-yr-old man with a history of insulin-dependent diabetes mellitus and previous myocardial infarction who underwent an emergent embolectomy of the right subclavian artery. The anesthesia was performed by field block using 2% plain lidocaine (200 mg) with intravenous sedation using midazolam 3 mg and fentanyl 100 μg. At the start of the procedure, a heparin infusion was started at a rate of 1000 U/h. The patient had an unremarkable intraoperative course, and the heparin infusion was discontinued at completion. On arrival at the postanesthesia recovery room, the patient's telemetry (lead II) had converted from normal sinus rhythm to atrial fibrillation. Electrocardiogram confirmed the atrial fibrillation, and no ischemic changes were noted. At this time, the patient had experienced no chest pain and was hemodynamically stable. Digitalis (1.0 mg) was administered intravenously over 4 h along with verapamil (7.5 mg) in 2.5-mg doses over 2 h. Heparin therapy was restarted at 1000 U/h after a 7500-U intravenous bolus. The patient was transferred to the coronary care unit, and a transthoracic echocardiogram was obtained to determine the etiology. This revealed mild hypokinesis with an ejection fraction of 40%. However, the transesophageal echocardiogram also revealed the additional presence of an intracardiac thrombus. Heparin therapy was reinstituted, and the cardiac rhythm converted to normal sinus 24 h later.

The purpose of this report was to demonstrate that an intracardiac thrombus is a treatable cause of atrial fibrillation in the postanesthesia recovery room and that transesophageal echocardiography was shown to be superior to the transthoracic echocardiogram in its detection (1,2).

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Book Reviews

The Obstetric Anesthesia Handbook

S. Datta. St. Louis: Mosby Yearbook, 1992, 353 pp, $34.95.

This textbook has two relatively unique features that are obvious on initial inspection. First, this book is written by one author, with the sole exception of the final chapter on the legal aspects of obstetric anesthesia, written by Robert M. Knapp, DO, JD. Second, this book is truly a handbook whose size, shape, and length fit the definition of a handbook. Both of these factors make a significant contribution to the success of this work.

There is complete uniformity of style, with little overlap and repetition, as well as a general theme and tone that prevails throughout the text. There is no doubt that this book grew out of routine lectures to students, residents, and research fellows. The text clearly and simply puts into words in an organized manner the kind of information that is passed along by a senior clinician to the next generation. The information is presented in a format that is easy to read and provides enough general discussion and controversies, yet comes to a conclusion and leads to potential management decisions. Although many of the topics discussed in this book have resulted in lengthy book chapters elsewhere (if not books in and of themselves), here the material is condensed in a very thoughtful and practical way. (The current trend seems to be that manuals grow into major books, and books grow into multiple volumes, if not seriously large tomes.) Although larger, more extensive texts clearly have their place as both teaching tools and as basic references, this handbook fills a unique need by providing practical, realistic information in a very accessible format.

When considering such a text, one must accept the obvious drawback that both the length and style do not permit lengthy descriptions of problems. On the other hand, for such a text it houses an incredible wealth of information that is both well organized and accessible. The index is particularly helpful in locating the information one wants quickly. This book is also unique in that it serves both as a truly excellent introduction to the area of obstetric anesthesia for the beginner and as an excellent reference for the occasional obstetric anesthesia practitioner who wishes to review a particular subject or unusual clinical problem. Its very brevity and straightforward nature make it ideal for both purposes. There are also adequate references, so that one can further explore particular problems in some detail. Surely this text is an excellent starting point for any number of controversial issues or specific problems.

The material covered is standard but complete. The introduction on maternal physiologic changes d
pregnancy, labor, and the postpartum period is ade
without being cumbersome. Even in sections tha
exceedingly brief—for example, local anesthetic pharm
ogy—the material presented is appropriate and exceed
current. The chapter on drug interactions and obs
anesthesia is particularly extensive and well organized
chapter on spinal opiates, although exceedingly
packs a great deal of information into very few p
However, it would have benefited from some sp
recommendations concerning monitoring of patients
have received spinal narcotics. Although there is appr
ate mention of delayed respiratory depression and
cerns with monitoring and caring for these patients,
cific recommendations are avoided.

In several sections of the text, there is solid inform
concerning the effects of anesthesia on the newbor
cluding neurobehavioral effects and the general probl
the effects of local anesthetics on the newborn. Throu
the text, be it systemic narcotics to newborn resuscit
there is appropriate emphasis and information pro
concerning the fetus and the newborn. Similarly, are
controversy are presented, with the several sides
considered. Very appropriate and practical comment
made concerning the use of a test dose in the "real wo
with several choices presented. On the other hand,
considering preeclampsia and the probable platelet
function, the author fails to present very specific guid
concerning the use of bleeding time and placeme
regional anesthetic in this group of patients. There a
course, benefits to presenting controversies without
ing to firm conclusions, particularly when there i
obvious firm answer to the problem. However, the clin
often seeks more specific guidelines or a stronger
point, both of which are occasionally missing in this

In conclusion, this is a well-written text that be
from a single author's viewpoint, style, and long hist
clinical experience. This book manages to be both exte
in scope and exceedingly practical and brief in pres
tion, without leaving the reader lost or simply read
glossary of terms. This book is a particularly worthy
tion to the library of the new resident or a pract
clinician who wants a quick and handy reference text

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Anesthesia and Organ Transplantation. Volume 29, No. 3 of the International Anesthesia Clinics

L. Firestone, ed. Boston: Little Brown, 1991, 159 pp, $81.00 (annual subscription of four issues).

Anesthesia and Organ Transplantation is a tightly written, enjoyable monograph that makes a valid effort to cover a broad area of anesthesia. Perhaps it is an oxymoron to say that this is a "comprehensive monograph," owing to the limitations of the medium; yet, the increase in transplantation procedures impacts greatly on common practice, and it is publications such as this that help keep us all up to date.

The opening chapter on organ donor care is excellent and suitably explains the hemodynamic and endocrine perturbations. Anesthesiologists play a key role in maintaining organ function, and the concept of the human body as an intensive care unit for the harvested organs is well related.

Subsequent chapters examine individual organ systems and their unique transplantation strategies: kidney, lung, heart, liver, pancreas. It is extremely interesting to observe techniques from other centers, although the distinct limitation of having one author for each chapter appears to segregate viewpoints. There is little reference to neighboring centers' techniques and a strong emphasis on the "Pittsburgh way." The sections on lung and liver transplantation are fascinating, and even the "nontransplant" anesthesiologist will learn key facts relating to common practice. The study of end-organ failure gives one a strong appreciation for intact physiology.

This is a valuable text; yet it would have been more complete with a review of basic immunology concepts to reacquaint the reader with relevant transplantation immunology. This could have led into a discussion of new immunosuppressive drugs; only a small paragraph is devoted to new work being done with FK506. Another area that was excluded from the book was a discussion of preservative solutions, an area that has impacted greatly on timing and outcome of transplantation operations.

Anesthesia and Organ Transplantation is a worthy monograph that covers a smattering of topics and techniques. Its brevity makes this a "quick" read but illustrates the incompleteness of the monograph style.

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Anesthesia for Organ Transplantation: A Society of Cardiovascular Anesthesiologists' Monograph

J. A. Fabian, ed. Philadelphia: J. B. Lippincott, 1992, 194 pp, $49.95.

The continued growth of organ transplantation and the increased longevity of transplant recipients will have an impact on many anesthesiologists. Those practicing in academic centers are often involved in the care of patients undergoing transplant surgery. As the population of transplant recipients grows, many will require surgical care in community hospital settings. This trend will make familiarity with the issues concerning the care of transplant patients requisite knowledge for all practicing anesthesiologists.

This monograph comprises 10 chapters by 22 contributors, including the editor. The chapters range in approach from a "cookbook" look at cardiac transplantation in children, as practiced at one institution, to a fascinating review of investigations into the physiologic alterations in the postcardiac transplant patient. The book fails to live up to its title by the lack of chapters on kidney or pancreas transplantation. Kidney transplantation, perhaps the least complicated transplant procedure, is certainly the most commonly performed currently. The monograph addresses heart and heart lung transplants; pediatric cardiac transplants; cardiovascular physiology after cardiac transplantation; mechanical cardiac assist devices and the total artificial heart; physiologic changes in the brain-dead organ donor; single-lung transplants; liver transplantation; immunosuppression; the use of cardiopulmonary bypass for organ transplantation; and, finally, ethical issues in organ transplantation.

The chapter on anesthetic considerations for liver transplantation is particularly well written. It includes a look at the altered physiology of the cirrhotic patient and a nice, concise review of the issues and concerns of each of the four stages of hepatic transplantation.

The chapter on ethical issues highlights recent developments that relate not to anesthesia, but rather to transplantation: Does unfairness result from allocating scarce organs based on criteria biased toward patients of white, European ethnicity? What are the implications of securing organs by means other than altruism? Do recipients perceive a change in their sense of self after organ transplantation, particularly recipients of animal organs? Should animals serve as organ donors? The chapter author addresses these issues well in terms of fairness and justice.

The monograph might have been improved with the inclusion of chapters on kidney and pancreas transplants and the deletion of a very superficial chapter on the use of cardiopulmonary bypass in organ transplantation. The book will serve as a good introduction to the field of anesthesia for organ transplantation and as a good starting point for further reading in this fast-growing area of our specialty.

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A Handbook of Paediatric Anaesthesia

Stephen J. Mather and David G. Hughes, eds. New York: Oxford University Press, 1991, 304 pp, $65.00.

This book is a short manual of pediatric anesthesia written by anesthetists in Bristol, England. The American reader will recognize some differences in the practice of pediatric anesthesia across the ocean, but by and large, these differences are small and not of major clinical significance, although, for the reader unfamiliar with British terminology, some of the names and terms will be difficult.

The value of this book is that it presents in 300 pages a well-written synopsis of much of the field of pediatric anesthesia. A glance at the chapter headings indicates that the usual topics are covered, including anatomy and physiology; pharmacology; pediatric anesthesia apparatus; monitoring in pediatric anesthesia; basic concepts of pediatric anesthesia practice; medical conditions with relevance to anesthesia; anesthesia for cardiac surgery; anesthesia for specialist surgery; day case anesthesia; anesthesia for radiologic procedures; pain management in children; acute airway problems; transport of critically ill children; and cardiopulmonary resuscitation. The information that is presented is sound and conforms in a general way with standard practice in the United States.

The disadvantage of this book, however, is the limited amount of material that can be presented in such a short space. Trainees who use the book are faced with a dilemma. They will find one approach for dealing with a problem but may not understand the rationale for the approach that is presented or the arguments advanced by others for the use of different techniques. Thus, if residents relied on this book alone, they would come away with a fairly "cookbook" approach to practicing pediatric anesthesia without understanding the principles on which sound medical judgments are made. In addition, the selection of references is spotty. In some cases, the original references are included, but this is not always the case. This reviewer believes that it would be difficult for the reader to delve deeply into any particular area on the basis of the references listed.

There are omissions of important material, partly as a result of trying to compress a complex field into a short space. For instance, there is no discussion of masseter spasm after succinylcholine. In other instances, statements are made without a reference for that statement; for example, if a child is anesthetized with a viremia, myocarditis can occur. Other important omissions are the failure to mention the use of phenylephrine or other techniques to raise blood pressure in patients who are having tetralogy of Fallot (Tet) spells, and the difference between primary and secondary ventricular septal defect.

In some areas, the British approach will be unfamiliar; examples are the use of cyclopropane for induction of anesthesia and the lack of use of oral midazolam. The discussion on anesthesia apparatus will be difficult for the American reader, because it largely concerns British apparatus, especially ventilators.

In summary, this book is well written and touches on the highlights of pediatric anesthesia. The problems center on the differences between British and American terminology and practice and the limited depth that is possible in a book of this length and type.

Donald C. Tyler, MD
Children's Hospital and Medical Center
Seattle, Washington

The Management of Acute Pain

G. Park and B. Fulton. New York: Oxford University Press, 1991, 166 pp, $59.95, ISBN 0-19-263016-4.

Much has been published recently on the management of acute pain, including journal articles, monographs, and texts aimed at comprehensive instruction in this area. Much less, though, has been written with the beginner in mind. *The Management of Acute Pain* is aimed at this audience. The authors describe the book as providing "simple, practical guidance" for junior medical students and nursing staff. Although the book effectively follows these guidelines, international differences in practice, drug names, and availability may limit its usefulness in the United States.

The book is structured in a logical fashion, with the first five chapters serving as an introduction. These chapters are well organized, well written, and easily read in a brief period of time, and they lay a solid groundwork for the chapters that follow. Several good tables are included that summarize and clarify the text (the one comparing various routes of drug administration is particularly useful).

The next several chapters in the book deal with the pharmacology and clinical application of opioid analgesics, presenting a very good overview of this area. Specific precautions and guidelines for each route of opioid administration are provided and reinforce the need for an organized and educated staff to care for patients receiving this therapy. The problem in this section and in subsequent pharmacology chapters is inherent in a book aimed at the British market. Drug names and drug availability are different than in this country. Also, the listed dose range for intrathecal morphine (0.5–1.0 mg) is higher than that usually used in the United States. This may explain why the authors caution against the use of intrathecal morphine, except in an intensive care unit-like setting.

The next chapter discusses the nonsteroidal antiinflammatory drugs in a brief but effective format. The advantages and disadvantages of this drug group are discussed, and comparative information on specific agents is included.

A chapter on local anesthetic pharmacology is well written and clinically relevant and includes the necessary section on the recognition and treatment of local anesthetic toxicity. Analgesic techniques involving local anesthetics are then briefly reviewed; however, nursing guidelines for "epidural top-up procedures" with local anesthetics describe a practice different from that common in the United States.

A discussion of the roles of nitrous oxide, transcutaneous nerve stimulation, and acupuncture in pain management completes the review of the most common pain-relief methods. The chapter on antiemetic drugs is well done, but, again, only a few of the drugs included are either available in the United States or in common usage. Some agents widely used in this country, such as hydroxyzine, are not even mentioned.

The book concludes with chapters on case studies in pain management and pain control in special situations. The discussion for each of the case studies is rather narrow and limited, with not enough emphasis on the advantages and disadvantages of various analgesic methods in a particular setting. A better written chapter could have effectively brought into focus the preceding content of the book, but as is, it is disappointing.

The final chapter on pain control in special situations deals with obstetrics and pediatrics. The pediatric section is useful, with a brief overview that discusses important differences in adult and pediatric pain. The obstetric pain section serves best to emphasize international differences in clinical practice. A description of the use of systemic opiates for managing the pain of labor and delivery makes up the bulk of this section, whereas epidural anesthesia is presented as a long list of disadvantages, with little positive said in its favor. This is certainly a misleading viewpoint for trainees in the United States.

The references in this book consist of chapter-specific reading lists rather than individual references. For the most part, these are well selected and reasonably recent.

In summary, consistent with the authors' aims, most of this book could be quite useful to medical students, junior housestaff, and nurses as an introduction to acute pain management. Georgette Love, RN, nurse specialist on the Acute Pain Service, University of Utah, summarized her opinion of the book by saying, "In general, I liked it. It has information that could have been useful to me when I started learning about pain. I will probably buy the book. . . . Lastly, the price tag ($59.95) is well above that expected for a book of this type; $30–$35 would seem reasonable."

Bradford D. Hare, MD
University of Utah School of Medicine
Salt Lake City, Utah

Books Received

Receipt of the books listed below is acknowledged. Selected books from this list will be reviewed in future issues of the Journal.

The Journal solicits reviews of new books from its readers. If you wish to submit a review, before proceeding please send a letter of intent, identifying the book in question, to Dr. Norig Ellison, Department of Anesthesia, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104. The Journal reserves the right of final decision on publication.

Cross AM, Janvier G, eds. *Tracheal Intubation*. Paris: Editions Pradel, 1992, 230 pp, $60.00, ISBN 0-683-08540-0.

Hall BA, Jones KA. *Anesthesia: A Comprehensive Review*. St. Louis: Mosby Year Book, 1992, 464 pp, $37.95, ISBN 0-8016-6930-8.

Kay PH, ed. *Techniques in Extracorporeal Circulation*. 3rd ed. Boston: Butterworth-Heinemann, 1992, 236 pp, $195.00, ISBN 0-7506-1991-2.

Power KJ. *Case Presentations Anesthesia & Intensive Care*. Boston: Butterworth–Heinemann, 1992, 127 pp, $29.95, ISBN 0-7506-0497-2.

Waugaman WR, Foster SD, Rigor BM, eds. *Principles and Practice of Nurse Anesthesia*. 2nd ed. Norwalk, Connecticut: Appleton & Lange, 1992, 897 pp, $90.00, ISBN 0-8385-7962-5.

Covering the Full Spectrum of Pain and Symptom Management

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Editor: **Russell K. Portenoy, M.D.,** New York, New York
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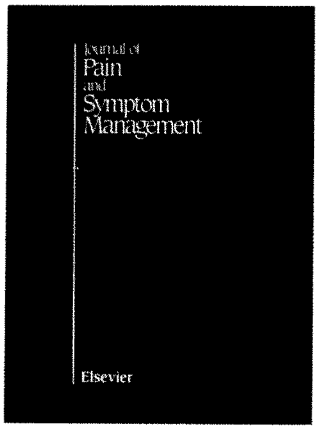

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1993

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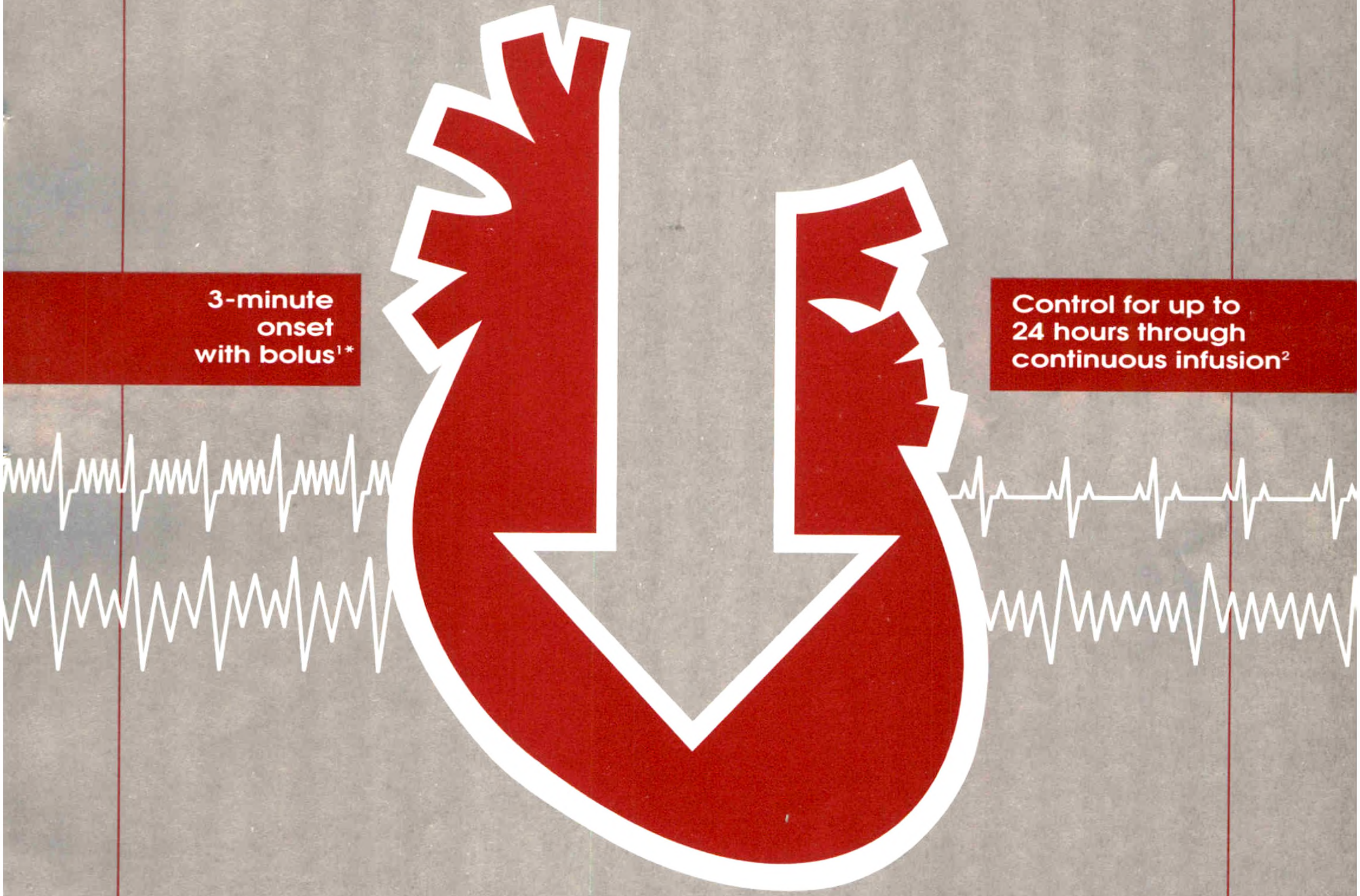

3-minute onset with bolus[1]*

Control for up to 24 hours through continuous infusion[2]

Heart rate control that is

FAST, SAFE, AND CONTINUOUS[1,2†]

Cardizem Injectable is indicated for temporary control of rapid ventricular rate during atrial fibrillation and flutter; rarely converts to normal sinus rhythm; should be used with continuous monitoring of ECG and blood pressure to avoid hypotension or bradycardia. Infusion rate/dose should be regulated accordingly. A defibrillator and emergency equipment should be readily available.

*Symptomatic hypotension (3.2%) or flushing (1.7%) occurs most often during or immediately following bolus injection.
†Contraindications: atrial fibrillation and flutter patients with WPW or short PR syndrome; sick sinus syndrome or second- or third-degree AV block, except with a functioning pacemaker; severe hypotension or shock; hypersensitivity; recent IV beta-blockers; ventricular tachycardia.

Please see the brief summary of prescribing information on an adjacent page.

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CARDIZEM® Injectable
(diltiazem hydrochloride)
BOLUS INFUSION

CONVENIENT DOSAGE

1 Beginning treatment as

BOLUS: 0.25 mg/kg actual body weight **over 2 minutes**

20 mg average patient

2 If response is inadequate, wait 15 minutes

BOLUS: 0.35 mg/kg actual body weight **over 2 minutes**

25 mg average patient

3 Treatment as

INFUSION:
10* to 15 mg/hr

*5 mg/hr may be appropriate starting infusion for some patients.

BRIEF SUMMARY

CARDIZEM® Injectable
(diltiazem hydrochloride)

INDICATIONS AND USAGE

CARDIZEM Injectable (diltiazem hydrochloride) is indicated for the following:

1. ***Atrial Fibrillation or Atrial Flutter.*** Temporary control of rapid ventricular rate in atrial fibrillation or atrial flutter. It should not be used in patients with atrial fibrillation or atrial flutter associated with an accessory bypass tract such as in Wolff-Parkinson-White (WPW) syndrome or short PR syndrome.
2. ***Paroxysmal Supraventricular Tachycardia.*** Rapid conversion of paroxysmal supraventricular tachycardias (PSVT) to sinus rhythm. This includes AV nodal reentrant tachycardias and reciprocating tachycardias associated with an extranodal accessory pathway such as the WPW syndrome or short PR syndrome. Unless otherwise contraindicated, appropriate vagal maneuvers should be attempted prior to administration of CARDIZEM Injectable.

The use of CARDIZEM Injectable for control of ventricular response in patients with atrial fibrillation or atrial flutter or conversion to sinus rhythm in patients with PSVT should be undertaken with caution when the patient is compromised hemodynamically or is taking other drugs that decrease any or all of the following: peripheral resistance, myocardial filling, myocardial contractility, or electrical impulse propagation in the myocardium.

For either indication and particularly when employing continuous intravenous infusion, the setting should include continuous monitoring of the ECG and frequent measurement of blood pressure. A defibrillator and emergency equipment should be readily available.

In domestic controlled trials in patients with atrial fibrillation or atrial flutter, bolus administration of CARDIZEM Injectable was effective in reducing heart rate by at least 20% in 95% of patients. CARDIZEM Injectable rarely converts atrial fibrillation or atrial flutter to normal sinus rhythm. Following administration of one or two intravenous bolus doses of CARDIZEM Injectable, response usually occurs within 3 minutes and maximal heart rate reduction generally occurs in 2 to 7 minutes. Heart rate reduction may last from 1 to 3 hours. If hypotension occurs, it is generally short-lived, but may last from 1 to 3 hours.

A 24-hour continuous infusion of CARDIZEM Injectable in the treatment of atrial fibrillation or atrial flutter maintained at least a 20% heart rate reduction during the infusion in 83% of patients. Upon discontinuation of infusion, heart rate reduction may last from 0.5 hours to more than 10 hours (median duration 7 hours). Hypotension, if it occurs, may be similarly persistent.

In the controlled clinical trials, 3.2% of patients required some form of intervention (typically, use of intravenous fluids or the Trendelenburg position) for blood pressure support following CARDIZEM Injectable.

In domestic controlled trials, bolus administration of CARDIZEM Injectable was effective in converting PSVT to normal sinus rhythm in 88% of patients within 3 minutes of the first or second bolus dose.

Symptoms associated with the arrhythmia were improved in conjunction with decreased heart rate or conversion to normal sinus rhythm following administration of CARDIZEM Injectable.

CONTRAINDICATIONS

CARDIZEM Injectable is contraindicated in:

1. Patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker.
2. Patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker.
3. Patients with severe hypotension or cardiogenic shock.
4. Patients who have demonstrated hypersensitivity to the drug.
5. Intravenous diltiazem and intravenous beta-blockers should not be administered together or in close proximity (within a few hours).
6. Patients with atrial fibrillation or atrial flutter associated with an accessory bypass tract such as in WPW syndrome or short PR syndrome.

   As with other agents which slow AV nodal conduction and do not prolong the refractoriness of the accessory pathway (eg, verapamil, digoxin), in rare instances patients in atrial fibrillation or atrial flutter associated with an accessory bypass tract may experience a potentially life-threatening increase in heart rate accompanied by hypotension when treated with CARDIZEM Injectable. As such, the initial use of CARDIZEM Injectable should be, if possible, in a setting where monitoring and resuscitation capabilities, including DC cardioversion/defibrillation, are present (see OVERDOSAGE). Once familiarity of the patient's response is established, use in an office setting may be acceptable.
7. Patients with ventricular tachycardia. Administration of other calcium channel blockers to patients with wide complex tachycardia (QRS $\geq$ 0.12 seconds) has resulted in hemodynamic deterioration and ventricular fibrillation. It is important that an accurate pretreatment diagnosis distinguish wide complex QRS tachycardia of supraventricular origin from that of ventricular origin prior to administration of CARDIZEM Injectable.

WARNINGS

1. **Cardiac Conduction.** Diltiazem prolongs AV nodal conduction and refractoriness that may rarely result in second- or third-degree AV block in sinus rhythm. Concomitant use of diltiazem with agents known to affect cardiac conduction may result in additive effects (see Drug Interactions). If high-degree AV block occurs in sinus rhythm, intravenous diltiazem should be discontinued and appropriate supportive measures instituted (see OVERDOSAGE).
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function and in patients with a compromised myocardium, such as severe CHF, acute MI, and hypertrophic cardiomyopathy, have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Administration of oral diltiazem in patients with acute myocardial infarction and pulmonary congestion documented by x-ray on admission is contraindicated. Experience with the use of CARDIZEM Injectable in patients with impaired ventricular function is limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM Injectable therapy may occasionally result in symptomatic hypotension (3.2%). The use of intravenous diltiazem for control of ventricular response in patients with supraventricular arrhythmias should be undertaken with caution when the patient is compromised hemodynamically. In addition, caution should be used in patients taking other drugs that decrease peripheral resistance, intravascular volume, myocardial contractility or conduction.
4. **Acute Hepatic Injury.** In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted following oral diltiazem. Therefore, the potential for acute hepatic injury exists following administration of intravenous diltiazem.
5. **Ventricular Premature Beats (VPBs).** VPBs may be present on conversion of PSVT to sinus rhythm with CARDIZEM Injectable. These VPBs are transient, are typically considered to be benign, and appear to have no clinical significance. Similar ventricular complexes have been noted during cardioversion, other pharmacologic therapy, and during spontaneous conversion of PSVT to sinus rhythm.

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. The drug should be used with caution in patients with impaired renal or hepatic function (see WARNINGS). High intravenous dosages (4.5 mg/kg tid) administered to dogs resulted in significant bradycardia and alterations in AV conduction. In subacute and chronic dog and rat studies designed to produce toxicity, high oral doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver, which were reversible when the drug was discontinued. In dogs, oral doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Dermatologic events progressing to erythema multiforme and/or exfoliative dermatitis have been infrequently reported following oral diltiazem. Therefore, the potential for these dermatologic reactions exists following exposure to intravenous diltiazem. Should a dermatologic reaction persist, the drug should be discontinued.

Drug Interactions. Due to potential for additive effects, caution is warranted in patients receiving CARDIZEM Injectable concomitantly with any agent(s) known to affect cardiac contractility and/or SA or AV node conduction (see WARNINGS).

As with all drugs, care should be exercised when treating patients with multiple medications. CARDIZEM undergoes extensive metabolism by the cytochrome P-450 mixed function oxidase system. Although specific pharmacokinetic drug-drug interaction studies have not been conducted with single intravenous injection or constant rate intravenous infusion, coadministration of CARDIZEM Injectable with other agents which primarily undergo the same route of biotransformation may result in competitive inhibition of metabolism.

Digitalis: Intravenous diltiazem has been administered to patients receiving either intravenous or oral digitalis therapy. The combination of the two drugs was well tolerated without serious adverse effects. However, since both drugs affect AV nodal conduction, patients should be monitored for excessive slowing of the heart rate and/or AV block.

Beta-blockers: Intravenous diltiazem has been administered to patients on chronic oral beta-blocker therapy. The combination of the two drugs was generally well tolerated without serious adverse effects. If intravenous diltiazem is administered to patients receiving chronic oral beta-blocker therapy, the possibility for bradycardia, AV block, and/or depression of contractility should be considered (see CONTRAINDICATIONS). ***Oral*** administration of diltiazem with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. In vitro, propranolol appears to be displaced from its binding sites by diltiazem.

Anesthetics: The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium blockers should be titrated carefully.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats at oral dosage levels of up to 100 mg/kg/day, and a 21-month study in mice at oral dosage levels of up to 30 mg/kg/day showed no evidence of carcinogenicity. There was also no mutagenic response in vitro or in vivo in mammalian cell assays or in vitro in bacteria. No evidence of impaired fertility was observed in a study performed in male and female rats at oral dosages of up to 100 mg/kg/day.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of oral doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended oral antianginal therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human oral antianginal dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. Diltiazem is excreted in human milk. One report with oral diltiazem suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

The following adverse reaction rates are based on the use of CARDIZEM Injectable in over 400 domestic clinical trial patients with atrial fibrillation/flutter or PSVT under double-blind or open-label conditions. Worldwide experience in over 1,300 patients was similar.

Adverse events reported in controlled and uncontrolled clinical trials were generally mild and transient. Hypotension was the most commonly reported adverse event during clinical trials. Asymptomatic hypotension occurred in 4.3% of patients. Symptomatic hypotension occurred in 3.2% of patients. When treatment for hypotension was required, it generally consisted of administration of saline or placing the patient in the Trendelenburg position. Other events reported in at least 1% of the diltiazem-treated patients were injection site reactions (eg, itching, burning)—3.9%, vasodilation (flushing)—1.7%, and arrhythmia (junctional rhythm or isorhythmic dissociation)—1.0%.

In addition, the following events were reported infrequently (less than 1%):

Cardiovascular:	Atrial flutter, AV block first degree, AV block second degree, bradycardia, chest pain, congestive heart failure, sinus pause, sinus node dysfunction, syncope, ventricular arrhythmia, ventricular fibrillation, ventricular tachycardia.
Dermatologic:	Pruritus, sweating.
Gastrointestinal:	Constipation, elevated SGOT or alkaline phosphatase, nausea, vomiting.
Nervous System:	Dizziness, paresthesia.
Other:	Amblyopia, asthenia, dry mouth, dyspnea, edema, headache, hyperuricemia.

Although not observed in clinical trials with CARDIZEM Injectable, other reactions associated with oral diltiazem may occur.

Product information as of October 1991

MARION MERRELL DOW INC.
PRESCRIPTION PRODUCTS DIVISION
KANSAS CITY, MO 64114

References: 1. Cardizem Injectable prescribing information.
2. Ellenbogen KA, Dias VC, Plumb VJ, Heywood JT, Mirvis DM. *J Am Coll Cardiol.* 1991;18:891-897.

CARDIZEM INJECTABLE...HEART RATE CONTROL THAT IS FAST, SAFE, AND CONTINUOUS

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Rank and pay commensurate with skills and experience. Faculty will serve at both a tertiary-care university hospital and a VA Medical Center. Candidates must be ABA certified, or in the examination process, and be eligible for a California state license. An Affirmative Action, Equal Opportunity Employer. Address correspondence with references and curriculum vitae to Steven J. Barker, PhD, MD, Chair, Department of Anesthesiology, University of California, Irvine Medical Center, 101 City Drive South, Route 81A, Orange, CA 92668.

930G/L

LOUISIANA STATE UNIVERSITY MEDICAL CENTER—SHREVEPORT

Faculty positions available for board certified/eligible anesthesiologists. Duties include patient care, resident and student teaching, supervision of CRNAs, research, and administrative responsibilities. Faculty rank and salary commensurate with experience. Please send curriculum vitae and names of three references to D. Richard Davis, II, MD, Associate Professor and Chairman, Department of Anesthesiology, LSU Medical Center—Shreveport, 1501 Kings Highway, Shreveport, LA 71130-3932. We are an Equal Opportunity/Affirmative Action Employer.

931G/L

ANESTHESIOLOGIST

Multispecialty group of 43 physicians adjacent to 165-bed hospital in need of BC/BE anesthesiologist. Located in West Texas City of 80,000 with excellent recreational activities. Salary guarantee with bonus based on production. Send CV to West Texas Medical Associates, 3555 Knickerbocker Road, San Angelo, TX 76904.

936H/A

CLASSIFIED ADS

Anesthesia & Analgesia makes available classified advertising space for those interested in obtaining positions or wishing to announce meetings, postgraduate courses, or other pertinent events. We require that all advertisements be relevant to the practice of anesthesia and analgesia, and we reserve the right to refuse advertisements that are not relevant.

Specifications. Ads should be typewritten on letterhead stationery; the text should be double-spaced, with the title or key phrase typed in capital letters. Enclose two photocopies with each ad. Display space (minimum ¼ page) is available through Pharmaceutical Media, Inc., 440 Park Avenue South, 14th floor, New York, NY 10016, telephone: (212) 685-5010, FAX: (212) 685-6126.

Rates. Ads cost $1.50 per word per insertion, with a minimum of 20 words. Abbreviations, dates, initials, post office box numbers, telephone numbers, years, and zip codes are considered one word each. There is an additional fee of $18.00 per insertion for box number ads.*

Payment. Full payment or institutional purchase order must accompany the copy for each ad. Ads received without a check or purchase order will be returned. (Make checks payable to Elsevier Science Publishing Company, Inc.)

Deadline. Copy must be received 7 weeks before publication date (i.e., by January 1 for the March issue); multiple-insertion ads are welcome. Ads may run up to 6 months per purchase order/payment. Please specify in which issue(s) your advertisement is to appear.

Send all ad copy, payments, and correspondence to: *Anesthesia & Analgesia*, Classified Ads, Desk Editorial, Elsevier Science Publishing Co., Inc., 655 Avenue of the Americas, New York, NY 10010.

*When responding to a box number ad, include the box number on all correspondence.

NEW ORLEANS

Louisiana State University Medical Center, Department of Anesthesiology, is seeking a board-certified anesthesiologist who is interested in directing publications and research. Outstanding opportunities for clinical studies are available. No night call, weekends, or holidays are required. Excellent salary and fringe benefits. Eligibility for Louisiana licensure is prerequisite. Please send curriculum vitae to M. Naraghi, MD, Professor and Chairman, LSU Department of Anesthesiology, 1532 Tulane Avenue, New Orleans, LA 70140. LSUMC is an EEO/AA employer.

937H/A

POSTDOCTORAL FELLOWSHIP

Background in clinical medicine or clinical research required for studies with patients with heart disease undergoing surgery. Cardiac function and ischemia assessed with ECG, Holter, and echocardiography monitoring. Working with cardiologists, epidemiologists, and anesthesiologists. Send CV and names of three references to Dennis T. Mangano, PhD, MD, Professor and Vice Chairman, Department of Anesthesia, University of California, San Francisco, 4150 Clement Street (129), San Francisco, CA 94121.

949H/L

BC/BE anesthesiologist for a 500-bed tertiary hospital in a Florida coastal city. Immediate opening. Liberal salary and early partnership. Send resume to Box 956I/L.

956I/L

BOISE, IDAHO—PAIN MANAGEMENT

MD/CRNA group seeking additional BC/BE anesthesiologist with pain fellowship or extensive pain experience for expanding pain clinic. Growing 250-bed hospital soon to be adding a Cancer Institute and Open Heart program. No OB. Great opportunity in progressive community (130,000) located in the foothills. Excellent for family and all types of year-round recreation. Partnership after 1 year. Please respond to William G. Binegar, MD, 6054 Emerald, Boise, ID 83704-8863.

957I/K

COASTAL NEW JERSEY—
ANESTHESIOLOGIST DESIRED

Immediate opening for BC or BE MD/DO to join an expanding group practice of 10 MDAs and 9 CRNAs covering a 500-bed regional medical center composed of two hospitals performing over 9000 anesthetics. All types of anesthesia except OH. Great opportunity for energetic well-trained individual. Unlimited opportunity and outstanding lifestyle in a family-oriented seashore community. Very competitive financial package. Please reply with CV to S. Hernberg, DO, Chairman, Department of Anesthesiology, 1925 Pacific Avenue, Atlantic City, NJ 08401.

958I/L

Anesthesiologist to join group consisting of eight anesthesiologists and two CRNAs. Must be board eligible or board certified. Established PC with many fringe benefits in effect. Send CV to Associated Anesthesiologists of Saginaw, PC, 3121 Davenport, Saginaw, MI 48602 or call (517) 791-2150.

959I/K

PHILADELPHIA, PA.

BC/BE anesthesiologist to join physician/CRNA group in a private, university-affiliated, center-city, tertiary-care hospital. No obstetrics, trauma, or pediatrics. Fellowship experience in open heart anesthesia required. Competitive salary, benefits, and potential for partnership is included. Respond with CV to Box 965I/K.

965I/K

UCSF PEDIATRIC ANESTHESIOLOGY FELLOWSHIP

The Departments of Anesthesia at the University of California, San Francisco and Children's Hospital of Northern California, Oakland, California are jointly offering two 1-year clinical fellowship positions (CA-4) in pediatric anesthesiology beginning *July 1993*. The fellowship will include extensive operating room experience in all pediatric subspecialties in both institutions and critical care medicine exposure for both neonates, older infants, and children. The fellows will spend 6 months in each institution. Send inquiries to Dolores Scholz, Postdoctoral Coordinator, Department of Anesthesia, University of California, San Francisco, Box 0648, San Francisco, CA 94143-0648.

967I/L

ANESTHESIOLOGIST

Department of Anesthesiology at the SUNY Health Science Center in Syracuse, N.Y. is recruiting faculty at the instructor and assistant and associate professor levels. Qualified individuals with a strong academic commitment in all types of anesthesia, critical care, and pain management are sought. SUNY Health Science Center is a tertiary-care center and provides clinical services also to the Syracuse Veterans Administration Hospital. Rank and salary are commensurate with experience. Must be board certified or board eligible and possess a New York State medical license. Please send letter, curriculum vitae, names, addresses, and phone numbers of three references to Enrico M. Camporesi, MD, Professor and Chairman, Department of Anesthesiology, SUNY Health Science Center, Syracuse, NY 13210. The State University of New York Health Science Center is an Equal Opportunity/AA Employer.

968I/K

UNIVERSARY OF CALIFORNIA, DAVIS—
Assistant Professor/Associate Professor/Full Professor

Department of Anesthesiology, University of California, Davis, Medical Center is recruiting for two (2) faculty positions at all ranks. These positions require experience in teaching and clinical training, as well as clinical research. Both positions require demonstrated experience, training, and certification in (1) Critical Care to join two other faculty covering ICU 2–3 months per year; (2) Transplant; and (3) General Anesthesia. These positions are in the non-tenured track. Rank and salary are commensurate with experience and based on the UCD School of Medicine Faculty Compensation Plan. Must be board certified or board eligible in anesthesiology, and a California medical license is required. Send curriculum vitae, bibliography, copies of publications, and *the names of three (3) references* to: Dennis Fung, MD, Acting Chairman, Department of Anesthesiology, University of California, Davis, 2315 Stockton Boulevard, Room 2304, Sacramento, CA 95817. Positions are open until filled but not later than December 31, 1992. The University of California, Davis is an Equal Opportunity/Affirmative Action Employer with a strong institutional commitment to the achievement of diversity among its faculty and staff. In that spirit, we are particularly interested in receiving applications from persons of under-represented groups, including women, ethnic minorities, disabled veterans, Vietnam-era veterans, and handicapped persons.

970I/K

ARKANSAS

Pediatric anesthesia fellowship to begin July 1, 1993. Broad-based training in pediatric anesthesia includes experience in cardiac, pain management, and critical care. Active research program. Prefer applicants who have completed CA-3 level in approved residency program. Must be eligible for Arkansas licensure. Send curriculum vitae to Raeford E. Brown, Jr., MD, Chief, Division of Pediatric Anesthesia, Arkansas Children's Hospital, 800 Marshall Street, Little Rock, AR 72202-3591. An Equal Opportunity Employer.

973I/K

ILLINOIS

Thirty-two physician, well-established, single-specialty group of anesthesiologists seeks additional anesthesiologists. Challenging, broad-based practice encompasses all surgical subspecialties at three hospitals and three ambulatory facilities. Excellent benefits with early partnership. Please send CV to Associated Anesthesiologists, S.C., 5401 North Knoxville, Suite #49, Peoria, IL 61614.

979J/C

MID-SOUTH: ANESTHESIOLOGIST
Immediate opening for BC/BE anesthesiologist at a modern 600-bed teaching hospital and major referral center located in the mid-south. Practice includes cardiac, thoracic, vascular, and general anesthesia as well as intensive care. No obstetrics or pediatrics. Group is to consist of six (6) doctors and 18 CRNAs. Please reply to Clifton W. Emerson, MD, Cardiovascular Anesthesiologists, P.C., 4230 Harding Road, Suite 509, Nashville, TN 37205. Please enclose your current CV.

980J/L

FELLOWSHIP—CARDIAC ANESTHESIOLOGY
CA-3 or CA-4 fellowship position now available in cardiac anesthesia. Busy open heart and vascular service. Opportunity for OR, cath lab, ICU, and clinical research. Excellent salary/benefit package. Send inquiries with CV to Anthony A. Ascioti, MD, Department of Anesthesiology, St. Joseph's Hospital Health Center, 301 Prospect Avenue, Syracuse, NY 13203.

984J/A

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
Faculty position available for board certified/eligible anesthesiologist whose primary clinical responsibilities will be in UCSF's ambulatory surgery facility. Applicants must have at least 5 years of postgraduate training and research experience in the outpatient area. Responsibilities emphasize clinical research, but also include patient care, resident and student teaching, and administrative responsibilities. A California medical license or eligibility for licensure is required. Please forward curriculum vitae to Martin S. Bogetz, MD, Medical Director, UCSF Surgery Center, 400 Parnassus Avenue (A3), San Francisco, CA 94143-0368; (415) 476-8384. The University of California is an Equal Opportunity Affirmative Action Employer.

985JK

PEDIATRIC ANESTHESIA
University of California, San Francisco has faculty positions available for board certified/eligible anesthesiologists with primary interest in pediatric anesthesia. Must have at least 5 years of postgraduate training, including clinical care and research training specific to pediatric patients. Duties include patient care, teaching, research, and administrative responsibilities. California medical license or eligibility for licensure is required. Please forward curriculum vitae and three references to Ronald D. Miller, MD, Professor and Chairman, Department of Anesthesia, UCSF, 521 Parnassus Avenue, Box 0648, Room C-455, San Francisco, CA 94143-0648. The University of California is an Equal Opportunity Affirmative Action Employer.

986JK

LIVER TRANSPLANTATION ANESTHESIA
University of California, San Francisco has faculty positions available for board certified/eligible anesthesiologists with primary interest in liver transplantation. Must have at least 5 years of postgraduate training, including clinical care and research training specific to liver transplant patients. Duties include patient care, teaching, research, and administrative responsibilities. California medical license or eligibility for licensure is required. Please forward curriculum vitae and three references to Ronald D. Miller, MD, Professor and Chairman, Department of Anesthesia, UCSF, 521 Parnassus Avenue, Box 0648, Room C-455, San Francisco, CA 94143-0648. The University of California is an Equal Opportunity Affirmative Action Employer.

987JK

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
Faculty position available in Anesthesia and Critical Care. Applicant must be BC/BE in anesthesia and critical care medicine. Applicant must have at least 5 years of postgraduate training, including research or other intensive care clinical training. Duties include patient care, resident and student teaching, research or specialized clinical activity, and administrative responsibilities. California medical license or eligibility for licensure is required. Send correspondence, curriculum vitae, and list of professional referees to Neal H. Cohen, MD, MPH, MS, Professor and Vice Chairman, Department of Anesthesia, 521 Parnassus Avenue, C450, University of California, San Francisco, CA 94143-0648. The University of California is an Equal Opportunity Employer.

988JK

ANESTHESIOLOGIST
Opening for BC/BE anesthesiologist to join MD/CRNA group in small midwestern university town. Area abounds in lakes, forests, wildlife, and recreational activities. Within easy driving distance to large metropolitan area. Working environment very stable and congenial. All surgical specialties represented except hearts and neuro. Salary commensurate with experience. Please reply with CV to Box 990K/D.

990K/D

ANESTHESIOLOGIST
BC/BE to join a 10-member fee-service group practice in a 350-bed community hospital plus free-standing surgery center in south central Pa. All surgical subspecialties except OH. Competitive salary, benefits leading to partnership. Fine suburban area with easy access to major metropolitan areas; excellent schools, many cultural and outdoor activities. Reply to Box 991K.

991K

MICHIGAN
BE/BC anesthesiologist to join busy 3 MD/7 CRNA group in southeastern Michigan lakeside community of 75,000. Excellent schools and family environment within 35 minutes of three large metropolitan areas. No open heart, minimal neuro. Salary and attractive benefit package first 24 months based on experience, leading to partnership offer. Send curriculum vitae and two references to Box 992K/B.

992 K/B

PAIN MANAGEMENT TRAINING: Changing directions?
Enter the highly gratifying specialty of Pain Management, offering both great professional and significant financial satisfaction. Six to twelve months training program is offered in a busy private practice pain center. Duration of training program depends on previous training in pain management. Our center provides a combination of extensive clinical experience in a wide variety of procedures, medical and psychological management of pain, and unique exposure to the business and administrative aspects of a large private practice pain management center. Appropriate candidates may be offered staff positions after training. For more information send CV to: "Pain Training," P.O. Box 802314, Dallas, TX 75380-2314. Attention: Medical Director.

993K

NEW YORK
CA-3 and CA-4 positions at Memorial Sloan-Kettering Cancer Center beginning July 1993. Advanced clinical and clinician-investigator opportunities available in critical care medicine, pain management, and anesthesia for thoracic surgery. Send CV and summary of career goals to Roger S. Wilson, MD, Chairman, Department of Anesthesiology and Critical Care Medicine, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021.

994KL

BC Anesthesiologist, 44, experienced in all techniques including OB, regional, and invasive monitoring seeks quality group or individual practice. Good references. Call (216) 372-5959.

995K/A

ANESTHESIOLOGISTS
Temple University School of Medicine has full-time faculty positions available for

board-eligible anesthesiologists with training in a subspecialty area (Cardiac Anesthesia, Critical Care and/or Pain). Faculty rank will be commensurate with experience. Duties include patient care, teaching, and research. Send curriculum vitae to Christer Carlsson, MD, PhD, Chairman, Department of Anesthesiology, Temple University School of Medicine, Broad & Ontario Streets, Philadelphia, PA 19140. An Equal Opportunity, Affirmative Action Employer.

996KL

CONTINUING EDUCATION SOCIETY

1993 Scientific Foundations of Anesthesia Board Reviews. Written courses: Jan 2–9; Mar 6–13; May 1–8; June 19–26. Oral courses: Feb 27–Mar 6, Apr 3–10. For more information call (800) 344-2093.

997K/J

PAIN FELLOWSHIP

The Pain Evaluation and Treatment Institute of the University of Pittsburgh Medical Center is offering 1-year CA-4 pain fellowships beginning January or July 1993. The fellowship offers experience, teaching, and research opportunities in outpatient and hospital-based pain therapy. Invasive, pharmacologic, and nonpharmacologic modalities are employed in a wide variety of clinical settings with emphasis on interdisciplinary management. Rotations in a regional anesthesia clinic, acute pain service, cancer pain service, and outpatient chronic pain rehabilitation program provide collaboration with a variety of dedicated pain specialists.

Direct inquiries to Brett Stacey, MD, Medical Director, Pain Evaluation and Treatment Institute, Baum Boulevard at Craig Street, Pittsburgh, PA 15213.

998K

UNIVERSITY OF PITTSBURGH MEDICAL CENTER

The Pain Evaluation and Treatment Institute is seeking additional faculty for our expanding in- and out-patient pain services. We manage acute, chronic, and cancer pain patients in an interdisciplinary fashion, utilizing all modalities of treatment. Teaching and research activities are well funded and supported by the department and university. Clinical anesthesia commitments are flexible depending on the needs of the applicant. Applicants must have completed a pain fellowship or have a similar background, be board certified or board eligible, be able to obtain a Pennsylvania license, and be interested in teaching and clinical research.

Direct inquiries to Brett Stacey, MD, Medical Director, Pain Evaluation and Treatment Institute, Baum Boulevard at Craig Street, Pittsburgh, PA 15213.

999K

ANESTHESIOLOGIST BE/BC to provide physician anesthesia at an academic medical center. Flexible schedule, no call. TJU is an Affirmative Action/Equal Opportunity Employer. Interested parties should contact: Joseph L. Seltzer, MD, Professor and Chairman, Department of Anesthesiology, Thomas Jefferson University, Philadelphia, PA 19107.

1000K/A

FELLOWSHIP—OBSTETRIC ANESTHESIA

Fellowship year emphasizing clinical/basic research. Resident teaching and high-risk clinical care included. Please send letter with CV and references (3) to Harvey Carp, PhD, MD, Department of Anesthesiology, Oregon Health Sciences University, 3181 S.W. Sam Jackson Park Road, Portland, Oregon 97201. Telephone: (503) 494-5223; Fax: (503) 494-4588.

1001K/A

ANESTHESIOLOGIST

Marshfield Clinic Department of Anesthesiology is seeking a BC/BE anesthesiologist with training or experience in pain management to join its 20 anesthesiologists and 17 nurse anesthetists. Pain Management Team and support specialties are in place. This practice would be split between pain management and hospital OR. Excellent compensation package. Pleasant semirural midwest community of 20,000. Please respond with cover letter, CV, and names of references to Debra K. Schuster, MD, Department of Anesthesiology, Marshfield Clinic, 1000 North Oak Avenue, Marshfield, WI 54449 or call collect at (715) 387-7179. EOE/AAM/F/H/V.

1002K

CHAIRMAN—DEPARTMENT OF ANESTHESIOLOGY

The Deborah Heart and Lung Center, a 155-bed acute care facility specializing in cardiac, pulmonary, and vascular diseases, is seeking applicants for the position of Chairman of the Department of Anesthesiology. Position entails overseeing the clinical activities of an 8 MD/8 CRNA/4 resident-fellow group, maintaining academic university affiliation, and stimulating research endeavors. The applicants must be board certified in anesthesiology, licensed in the state of New Jersey, and experienced in the administration of an active clinical service dealing with complex pediatric and adult cardiac patients. Skills in research and resident education also desired. Send your CV and the names and addresses of three academic references to Vladir Maranhao, MD, Vice President, Medical Affairs Deborah Heart and Lung Center, Browns Mills, NJ 08015.

1003K

PEDIATRIC ANESTHESIOLOGIST: FACULTY POSITIONS

The Department of Anesthesiology, Baylor College of Medicine and its Pediatric Anesthesiology Division at Texas Children's Hospital are recruiting faculty. 8500 cases per year span the range of pediatric anesthesia. Our training program is for CA-2 level and beyond. Qualified pediatric anesthesia specialists can combine clinical/academic practice in a growing, academically oriented division with hospitable living in the economically resurgent climate of Houston, Texas. Successful applicants will be board certified in anesthesiology or in the board examination process and eligible for a Texas license. A minimum of 1-year pediatric anesthesia specialty training at the CA-4 level or beyond is expected. Equivalents are these: current clinical practice limited to pediatric anesthesia or BC, pediatrics. Research interests desirable with encouragement through appropriate amounts of nonclinical time. Salary levels are competitive. Baylor is an Equal Opportunity Employer. Send CV and three references to Burdett S. Dunbar, MD, Chief, Pediatric Anesthesiology, Texas Children's Hospital, 6621 Fannin, Mail Code 2-1495, Houston, TX 77030.

1004K

FELLOWSHIP TRAINING, PEDIATRIC ANESTHESIOLOGY

Baylor College of Medicine, Department of Anesthesiology and its Pediatric Anesthesiology Division at Texas Children's Hospital offer 1- or 2-year subspecialty training in pediatric anesthesiology beginning January 1993. Texas Children's Hospital, a 300-bed facility, is a primary academic affiliate of Baylor College of Medicine. Current case load, 8500 cases per year, spans the range of pediatric anesthesia. Opportunities exist for experience in neonatal critical care, critical care medicine, operating room, pain medicine, and research. Requirements: satisfactory completion of AMA-RRC approved residency; currently in the ABA certification process; eligibility for unrestricted medical license, Texas. Salary: $30,000. Send current CV and three references to Burdett S. Dunbar, MD, Chief, Pediatric Anesthesiology, Texas Children's Hospital, 6621 Fannin Street, Mail Code 2-1495, Houston, TX 77030.

1005K

FELLOWSHIP—PEDIATRIC ANESTHESIOLOGY

The Department of Anesthesiology for the Medical College of Wisconsin is accepting applications for 12-month subspecialty training in pediatric anesthesiology beginning July 1, 1993 (CA-3 and CA-4 positions are available). Experience and training will include all aspects of pediatric anesthesiology including cardiac anesthesia and pain management. Opportunity also is provided for clinical research and critical care experience. Inquiries, CV, and references should be sent to Stephen P. Pontus, MD, Section of Pediatric Anesthesiology, Children's Hospital of Wisconsin, PO Box 1997, MS 735, Milwaukee, Wisconsin 53201. Equal Opportunity/Affirmative Action Employer M/F/D.

1008KL

YALE UNIVERSITY DEPARTMENT OF ANESTHESIOLOGY, NEW HAVEN, CONNECTICUT

Applications are invited for faculty positions at Assistant Professor and Associate Professor levels. These positions offer excellent opportunities to develop an academic career in a department with excellent clinical and research resources. Positions to be filled require qualified candidates in general anesthesia and some positions require cardiovascular or pediatric anesthesia subspecialty training and experience. Please respond prior to December 31, 1992. Send CV to Paul G. Barash, MD, Professor and Chairman, Department of Anesthesiology, Yale University School of Medicine, PO Box 3333, New Haven, CT 06510. Yale University School of Medicine is an Affirmative Action/Equal Opportunity Employer.

1009K

EAST CENTRAL INDIANA

Anesthesiologist needed to join group of nine MDs serving two large hospitals. No open heart or neuro. Fee for service; low malpractice. Located 45 miles from downtown Indianapolis. Contact (317) 378-6654 or reply to PO Box 4237, Anderson, IN 46013.

1010KL

UNIVERSITY OF ARIZONA, DEPARTMENT OF ANESTHESIOLOGY, PHOENIX CAMPUS AT MARICOPA MEDICAL CENTER

Is growing and seeking qualified, board certified/board eligible anesthesiologists for the following positions: Pediatric Anesthesia, Critical Care, Cardiac Anesthesia, and Directors of Pain Management and of Respiratory Therapy. Responsibilities include patient care, teaching, research, and administration. Please forward curriculum vitae and three references to Jerry M. Calkins, PhD, MD, Clinical Professor and Chairman, Department of Anesthesiology, Maricopa Medical Center, 2601 East Roosevelt, PO Box 5099, Phoenix, AZ 85010. Equal Opportunity Employer.

1011K/D

NORTHCENTRAL PENNSYLVANIA

BC/BE Anesthesiologist to direct an Anesthesia Department of three CRNAs at a progressive rural community hospital. Located in the beautiful mountains of Potter County, well known for outdoor recreational activities, this community is an ideal setting for the family. Competitive salary guarantee. Excellent practice opportunity. Please send CV to Jan Freeman Knisley, Physician Recruiter, Charles Cole Memorial Hospital, RR1, Box 205, Coudersport, PA 16915-9762; or call (814) 274-9300, ext 486, or (814) 274-0229.

1012K/A

WANTED: TWO ANESTHESIOLOGISTS at the Instructor or above level. Must have an MD degree, completed a 4-year residency in anesthesiology, have documentation in research fellowship or postgraduate training, and be board certified or board eligible. The positions have an anticipated starting date of February 1, 1993 or later. Stipend negotiable and dependent on credentials. Interested parties should forward letter including board status, curriculum vitae, and bibliography to Salvatore R. Goodwin, MD, Search Committee Chairman, Department of Anesthesiology, University of Florida College of Medicine, PO Box 100254, Gainesville, FL 32610-0254. Application deadline for position is January 15, 1993. Equal Employment Opportunity/Affirmative Action Employer.

1013KL

WANTED: CLINICAL ANESTHESIOLOGIST at the Clinical Instructor, Clinical Assistant Professor or Clinical Associate Professor level. Must have an MD degree, completed a 4-year residency in anesthesiology, have documentation in research fellowship or postgraduate training, and be board certified or board eligible. The position has an anticipated starting date of February 1, 1993 or later. Stipend negotiable and dependent on credentials. Interested parties should forward letter including board status, curriculum vitae, and bibliography to Salvatore R. Goodwin, MD, Search Committee Chairman, Department of Anesthesiology, University of Florida College of Medicine, PO Box 100254, Gainesville, FL 32610-0254. Application deadline for position is January 15, 1993. Equal Employment Opportunity/Affirmative Action Employer.

1014KL

PEDIATRIC ANESTHESIOLOGIST

The Nemours Children's Clinic, a pediatric tertiary-care subspecialty clinic, located on the St. Johns River in Jacksonville, Florida, is seeking a staff pediatric anesthesiologist. Nemours is a partner in a consortium, including the new Children's Hospital, for the development of a Regional Pediatric Medical Center. In order to provide innovative services and additional patient care in a new Children's Hospital, Nemours is expanding its Department of Anesthesiology. Candidates must be BC/BE in anesthesiology, with a pediatric anesthesiology fellowship or the equivalent in experience. Proximity to First Coast beaches, cultural and recreational opportunities, and year-round mild climate, as well as an opportunity for professional growth and participation in research and resident education, make this a very desirable employment choice. The recruiting deadline is 2/1/93. Interested applicants should send CV to Dr. Richard Helffrich, Jr., Chairman, Search Committee, Nemours Children's Clinic, 807 Nira Street, Jacksonville, FL 32207, (904) 390-3766. Nemours is an Equal Opportunity Employer.

1015KL

PAIN MANAGEMENT CAREER OPPORTUNITY—FLORIDA/TEXAS

New career opportunity in pain management for anesthesiologist. For more information call Richard Tinsley, Multidisciplinary Pain Systems, Inc., 1/800/365-0619.

1016K/A

PAIN MANAGEMENT SPECIALIST seeking a BE/BC anesthesiologist with pain fellowship. Join young progressive anesthesiologist in postop, chronic and acute pain management. Emphasis on lifestyle. Option to work four to twelve months per year. Four season climate in rural setting. Send CV to Box 1017 K/A.

1017K/A

ANESTHESIOLOGIST 8 yr experience in all general and regional anesthesia. Comfortable with all types of anesthesia. Fellowship in OB. All offers considered, willing to relocate. Licensed in NJ, NY, Florida, Illinois, Pennsylvania, Michigan, Iowa. Reply to Box 1018 K/B.

1018K/B

ANESTHESIOLOGIST

Board certified. Experienced in invasive monitoring and OB; capable of taking over as Chief of six MDs and two CRNAs in this group practice of 250-bed Community Hospital in southern New England. Kindly send replies to Anesthesia Group Service, PO Box 7879, Cumberland, RI 02864.

1019KL

UNIVERSITY OF ARIZONA

Expanding University program creates exciting opportunities for new faculty, both academic (tenure) and clinical tracks. Applicants must be interested in academic career. Interested particularly in cardiac, obstetric, ICU, and pediatric subspecialties. An AA/EOE. Contact: Burnell R. Brown, Jr., MD, PhD, Department of Anesthesiology, Arizona Health Sciences Center, Tucson, AZ 85724. Closing date: 6/30/93 or until position is filled.

1020K/G

ANESTHESIOLOGISTS

Albany Medical College has immediate openings for BC/BE anesthesiologists to join our staff of 30 MDs, and over 60 CRNAs and residents, to provide team-approach anesthesia care for all types of cases. Interest in teaching and research is highly desirable.

We are a 660-bed, tertiary-care facility with 20 newly renovated OR suites equipped with state-of-the-art instrumentation.

Our highly competitive benefits package includes generous leave time, health and dental plan, pension and disability plan, malpractice and life insurance. Interested applicants should send CV and three references to: Philip D. Lumb, MBBS, Professor and Chairman, Albany Medical College, Department of Anesthesiology, Mail Code A-131, Albany, New York 12208.

1021KAC

OB anesthesiologist sought for large university-affiliated hospital. Approximate 300 deliveries a month with many high risk. In-house neonatologists. Reasonable call schedule with competitive compensation package and partnership after 1 year. Send or fax CV to Barney S. H. Feinstein, MD, Chairman, Department of Anesthesia, Washington Hospital Center, 110 Irving Street, NW, Washington, DC 20010; Fax number (202) 877-5564.

872CEGIK

ANESTHESIOLOGIST/PAIN MANAGEMENT (PORTLAND, OREGON)

Northwest Permanente, P.C., a stable, multispecialty group providing care for 380,000 members of Kaiser Permanente, is seeking a BC/BE anesthesiologist to join a group of 9 anesthesiologists and 27 CRNAs at our 220-bed Sunnyside Medical Center, one of two Kaiser medical centers in the Portland area. Group provides full range of anesthesia services except for open heart.

Special interest: Pain Management, fellowship trained. Join two other trained MDs part-time in a growing Chronic Pain Clinic with dedicated time, clinical procedure-room space, and an OR block for fluoroscopy procedures. The department has ongoing research projects in both pain and anesthesia and is preparing a book manuscript on pain.

Stimulating professional environment, beautiful recreation area with easy access to mountains and beaches. Excellent salary and benefits including paid malpractice, sabbatical, two pension plans, and more. Please forward CV to Fred M. Nomura, MD, Regional Medical Center, NORTHWEST PERMANENTE, P.C., 2701 N.W. Vaughn, Suite 300, Portland, OR 97210-5398. EOE.

969IK

DON'T FAIL THE WRITTEN BOARDS!

Unique study program including memory devices, methods for improved retention, guessing techniques, etc. Practice questions with answers, explanations and references, new Keywords. Get MEDTEXT not imitations. Call 1-800-695-6301 for information 24 hours. Call 1-800-232-TEXT for orders. MC/V accepted.

933H/A

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The unique feature of these programs is the maximum class size of four students. Preparation for the written and oral exams are given separately in 3-day blocks in San Francisco and New York. FOR THE WRITTENS, techniques are taught for dealing with the multiple-choice questions. The basic sciences are stressed. FOR THE ORALS, the guided case discussions are stressed. Home study programs are provided. CALL (415) 321-1117.

763I/B

Dial 1-800/RENT-A-DOC

For anesthesiologists and CRNAs. We can provide you with quality locum tenens services to meet your specific coverage needs. Or work locum tenens with us for a change in both your practice and your lifestyle. ReplaceMed * 1-800/736-8236 * PO Box 640 * Michigan City, IN 46360.

832A/L

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Alfenta®
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Before prescribing, please consult complete prescribing information, of which the following is a brief summary.

CAUTION: Federal Law Prohibits Dispensing Without Prescription
DESCRIPTION: ALFENTA is a sterile, non-pyrogenic, preservative free aqueous solution containing alfentanil hydrochloride equivalent to 500 µg per ml of alfentanil base for intravenous injection. The solution, which contains sodium chloride for isotonicity, has a pH range of 4.0-6.0.
CONTRAINDICATIONS: ALFENTA (alfentanil hydrochloride) is contraindicated in patients with known hypersensitivity to the drug.
WARNINGS: ALFENTA SHOULD BE ADMINISTERED ONLY BY PERSONS SPECIFICALLY TRAINED IN THE USE OF INTRAVENOUS AND GENERAL ANESTHETIC AGENTS AND IN THE MANAGEMENT OF RESPIRATORY EFFECTS OF POTENT OPIOIDS. AN OPIOID ANTAGONIST, RESUSCITATIVE AND INTUBATION EQUIPMENT AND OXYGEN SHOULD BE READILY AVAILABLE. BECAUSE OF THE POSSIBILITY OF DELAYED RESPIRATORY DEPRESSION, MONITORING OF THE PATIENT MUST CONTINUE WELL AFTER SURGERY. ALFENTA (alfentanil hydrochloride) administered in initial dosages up to 20 µg/kg may cause skeletal muscle rigidity, particularly of the truncal muscles. The incidence and severity of muscle rigidity is usually dose-related. Administration of ALFENTA at anesthetic induction dosages (above 130 µg/kg) will consistently produce muscular rigidity with an immediate onset. The onset of muscular rigidity occurs earlier than with other opioids. ALFENTA may produce muscular rigidity that involves all skeletal muscles, including those of the neck and extremities. The incidence may be reduced by: 1) routine methods of administration of neuromuscular blocking agents for balanced opioid anesthesia; 2) administration of up to ¼ of the full paralyzing dose of a neuromuscular blocking agent just prior to administration of ALFENTA at dosages up to 130 µg/kg; following loss of consciousness, a full paralyzing dose of a neuromuscular blocking agent should be administered; or 3) simultaneous administration of ALFENTA and a full paralyzing dose of a neuromuscular blocking agent when ALFENTA is used in rapidly administered anesthetic dosages (above 130 µg/kg). The neuromuscular blocking agent used should be appropriate for the patient's cardiovascular status. Adequate facilities should be available for postoperative monitoring and ventilation of patients administered ALFENTA. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.
PRECAUTIONS: DELAYED RESPIRATORY DEPRESSION, RESPIRATORY ARREST, BRADYCARDIA, ASYSTOLE, ARRHYTHMIAS AND HYPOTENSION HAVE ALSO BEEN REPORTED. THEREFORE, VITAL SIGNS MUST BE MONITORED CONTINUOUSLY.
General: The initial dose of ALFENTA (alfentanil hydrochloride) should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining supplemental doses. In obese patients (more than 20% above ideal total body weight), the dosage of ALFENTA should be determined on the basis of lean body weight. In one clinical trial, the dose of ALFENTA required to produce anesthesia, as determined by appearance of delta waves in EEG, was 40% lower in geriatric patients than that needed in healthy young patients. In patients with compromised liver function and in geriatric patients, the plasma clearance of ALFENTA may be reduced and postoperative recovery may be prolonged. Induction doses of ALFENTA should be administered slowly (over three minutes). Administration may produce loss of vascular tone and hypotension. Consideration should be given to fluid replacement prior to induction. Diazepam administered immediately prior to or in conjunction with high doses of ALFENTA may produce vasodilation, hypotension and result in delayed recovery. Bradycardia produced by ALFENTA may be treated with atropine. Severe bradycardia and asystole have been successfully treated with atropine and conventional resuscitative methods. The hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required should be considered in the selection of a neuromuscular blocking agent. Following an anesthetic induction dose of ALFENTA, requirements for volatile inhalation anesthetics or ALFENTA infusion are reduced by 30 to 50% for the first hour of maintenance. Administration of ALFENTA infusion should be discontinued at leas 10-15 minutes prior to the end of surgery. Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists such as naloxone. Because the duration of respiratory depression produced by ALFENTA may last longer than the duration of the opioid antagonist action, appropriate surveillance should be maintained. As with all potent opioids, profound analgesia is accompanied by respiratory depression and diminished sensitivity to CO_2 stimulation which may persist into or recur in the postoperative period. Intraoperative hyperventilation may further alter postoperative response to CO_2. Appropriate postoperative monitoring should be employed, particularly after infusions and large doses of ALFENTA, to ensure that adequate spontaneous breathing is established and maintained in the absence of stimulation prior to discharging the patient from the recovery area.
Head Injuries: ALFENTA may obscure the clinical course of patients with head injuries.
Impaired Respiration: ALFENTA should be used with caution in patients with pulmonary disease, decreased respiratory reserve or potentially compromised respiration. In such patients, opioids may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration.
Impaired Hepatic or Renal Function: In patients with liver or kidney dysfunction, ALFENTA should be administered with caution due to the importance of these organs in the metabolism and excretion of ALFENTA.
Drug Interactions: Both the magnitude and duration of central nervous system and cardiovascular effects may be enhanced when ALFENTA is administered in combination with other CNS depressants such as barbiturates, tranquilizers, opioids, or inhalation general anesthetics. Postoperative respiratory depression may be enhanced or prolonged by these agents. In such cases of combined treatment, the dose of one or both agents should be reduced. Limited clinical experience indicates that requirements for volatile inhalation anesthetics are reduced by 30 to 50% for the first sixty (60) minutes following ALFENTA induction. The concomitant use of erythromycin with ALFENTA can significantly inhibit ALFENTA clearance and may increase the risk of prolonged or delayed respiratory depression. Perioperative administration of drugs affecting hepatic blood flow or enzyme function may reduce plasma clearance and prolong recovery.
Carcinogenesis, Mutagenesis and Impairment of Fertility: No long-term animal studies of ALFENTA have been performed to evaluate carcinogenic potential. The micronucleus test in female rats and the dominant lethal test in female and male mice revealed that single intravenous doses of ALFENTA as high as 20 mg/kg (approximately 40 times the upper human dose) produced no structural chromosome mutations or induction of dominant lethal mutations. The Ames *Salmonella typhimurium* metabolic activating test also revealed no mutagenic activity.
Pregnancy Category C: ALFENTA has been shown to have an embryocidal effect in rats and rabbits when given in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects could have been due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug. No evidence of teratogenic effects has been observed after administration of ALFENTA in rats or rabbits. There are no adequate and well-controlled studies in pregnant women. ALFENTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Labor and Delivery: There are insufficient data to support the use of ALFENTA in labor and delivery. Placental transfer of the drug has been reported; therefore, use in labor and delivery is not recommended.
Nursing Mothers: In one study of nine women undergoing post-partum tubal ligation, significant levels of ALFENTA were detected in colostrum four hours after administration of 60 µg/kg of ALFENTA, with no detectable levels present after 28 hours. Caution should be exercised when ALFENTA is administered to a nursing woman.
Pediatric Use: Adequate data to support the use of ALFENTA in children under 12 years of age are not presently available.
ADVERSE REACTIONS: The most common adverse reactions, respiratory depression and skeletal muscle rigidity, are extensions of known pharmacological effects of opioids. See CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS on the management of respiratory depression and skeletal muscle rigidity. Delayed respiratory depression, respiratory arrest, bradycardia, asystole, arrhythmias and hypotension have also been reported. The reported incidences of adverse reactions listed in the following table are derived from controlled and open clinical trials involving 1183 patients, of whom 785 received ALFENTA. The controlled trials involved treatment comparisons with fentanyl, thiopental sodium, enflurane, saline placebo and halothane. Incidences are based on disturbing and nondisturbing adverse reactions reported. The comparative incidence of certain side effects is influenced by the type of use, e.g., chest wall rigidity has a higher reported incidence in clinical trials of alfentanil induction, and by the type of surgery, e.g., nausea and vomiting have a higher incidence in patients undergoing gynecologic surgery.

Percent	ALFENTA (N=785)	Fentanyl (N=243)	Thiopental Sodium (N=66)	Enflurane (N=55)	Halothane (N=18)	Saline Placebo* (N=18)
Gastrointestinal						
Nausea	28	44	14	5	0	22
Vomiting	18	31	11	9	13	17
Cardiovascular						
Bradycardia	14	7	8	0	0	0
Tachycardia	12	12	39	36	31	11
Hypotension	10	8	7	7	0	0
Hypertension	18	13	30	20	6	0
Arrhythmia	2	2	5	4	6	0
Musculoskeletal						
Chest Wall Rigidity	17	12	0	0	0	0
Skeletal Muscle Movements	6	2	6	2	0	0
Respiratory						
Apnea	7	0	0	0	0	0
Postoperative Respiratory Depression	2	2	0	0	0	0
CNS						
Dizziness	3	5	0	0	0	0
Sleepiness/ Postoperative Sedation	2	8	2	0	0	6
Blurred Vision	2	2	0	0	0	0

*From two clinical trials, one involving supplemented balanced barbiturate / nitrous oxide anesthesia and one in healthy volunteers who did not undergo surgery.

In addition, other adverse reactions less frequently reported (1% or less) were: Laryngospasm, bronchospasm, postoperative confusion, headache, shivering, postoperative euphoria, hypercarbia, pain on injection, urticaria, and itching. Some degree of skeletal muscle rigidity should be expected with induction doses of ALFENTA.
DRUG ABUSE AND DEPENDENCE: ALFENTA (alfentanil hydrochloride) is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and therefore has the potential for being abused.
OVERDOSAGE: Overdosage would be manifested by extension of the pharmacological actions of ALFENTA (alfentanil hydrochloride) (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. No experience of overdosage with ALFENTA was reported during clinical trials. The intravenous LD_{50} of ALFENTA is 43.0-50.9 mg/kg in rats, 72.2-73.6 mg/kg in mice, 71.8-81.9 mg/kg in guinea pigs and 59.5-87.5 mg/kg in dogs. Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression. The duration of respiratory depression following overdosage with ALFENTA may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist should not preclude immediate establishment of a patent airway, administration of oxygen, and assisted or controlled ventilation as indicated for hypoventilation or apnea. If respiratory depression is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled ventilation. Intravenous fluids and vasoactive agents may be required to manage hemodynamic instability.
DOSAGE AND ADMINISTRATION: The dosage of ALFENTA (alfentanil hydrochloride) should be individualized in each patient according to body weight, physical status, underlying pathological condition, use of other drugs, and type and duration of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of ALFENTA should be determined on the basis of lean body weight. The dose of ALFENTA should be reduced in elderly or debilitated patients (see PRECAUTIONS). Vital signs should be monitored routinely. Protect from light. Store at room temperature 15°-30° C (59°-86° F).

JANSSEN
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March 1987, April 1988
U.S. Patent No. 4,167,574
49-7619902-M

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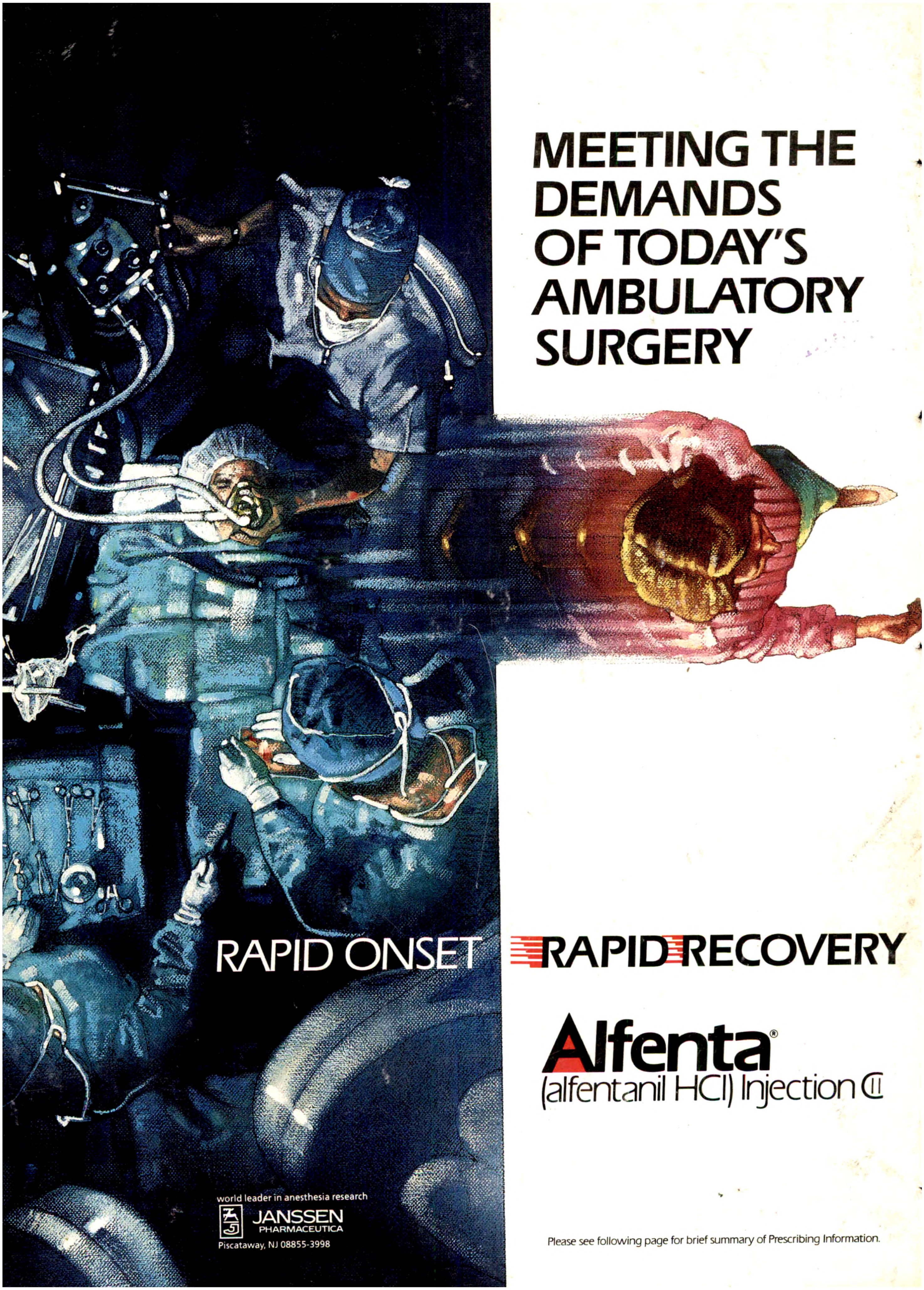

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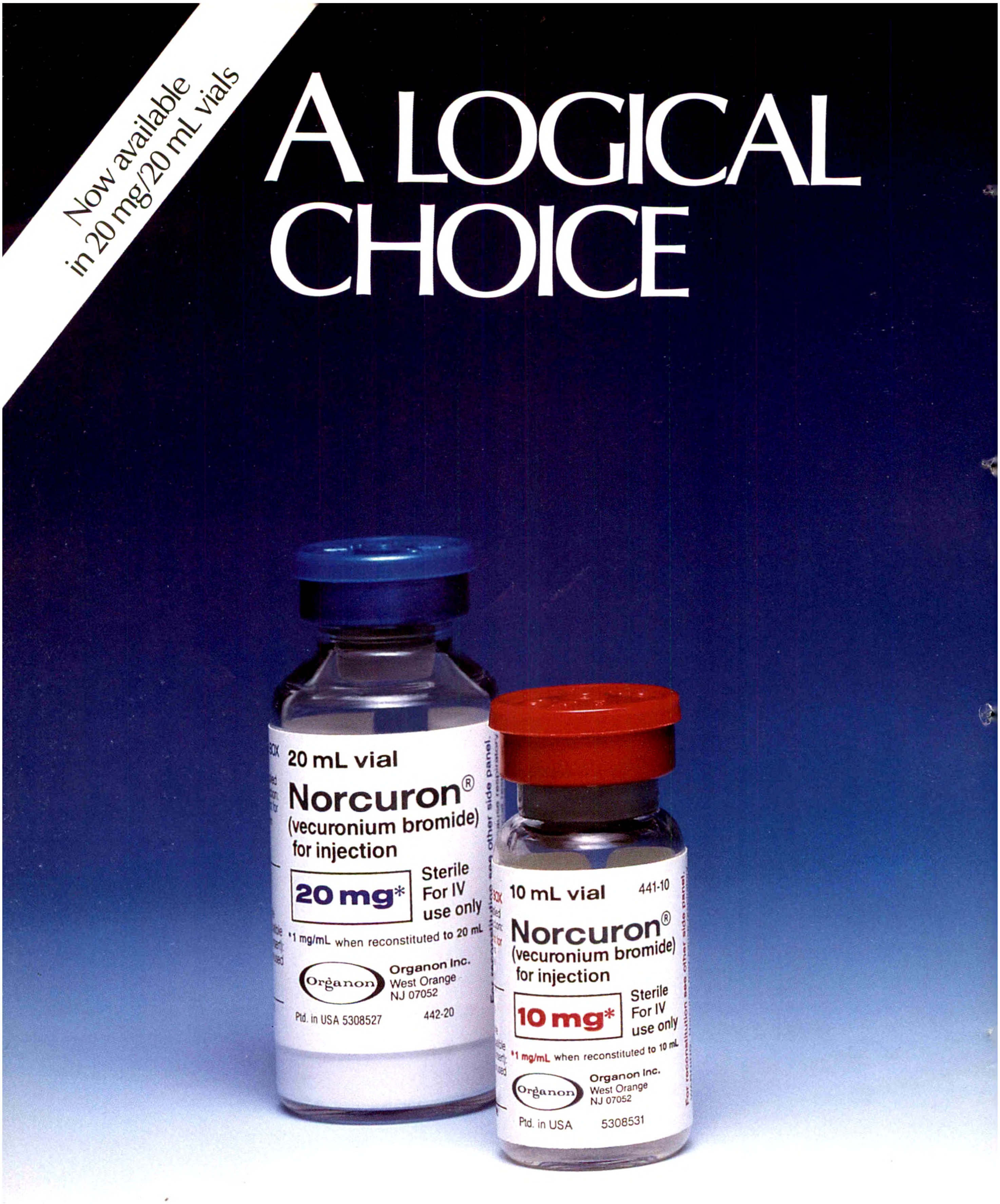
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HEMODYNAMICS	No significant variations in blood pressure, cardiac output, or systemic vascular resistance.[1]	Statistically significant variations in blood pressure, cardiac output, and systemic vascular resistance.[1] ($P<.05$)
HISTAMINE	Available clinical experience indicates that reactions commonly associated with histamine release are unlikely to occur.[1-4]	Precautions advised for patients in whom substantial histamine release would be hazardous (eg, clinically significant cardiovascular disease, asthma).[5]
RECOVERY To 25% of control To 95% of control	 25-40 min[3] 45-65 min[3]	 35-45 min[5] 60-70 min[5]
DOSING FLEXIBILITY	The initial recommended dose is 0.08-0.1 mg/kg. Dose can be increased up to 0.28 mg/kg for long cases without significant histamine release or related cardiovascular side effects.[1,3,4]	Initial recommended dose is 0.4-0.5 mg/kg. A moderate histamine release and significant falls in blood pressure have been seen following a dose of 0.5 mg/kg ($P<.05$) and 0.6 mg/kg.*[2,5,6]
STORAGE & SHELF LIFE	2-year shelf life in lyophilized form at room temperature.† Can be reconstituted with various IV solutions including Lactated Ringers.‡	2-year shelf life under constant refrigeration.† Upon removal from refrigeration to room temperature storage, use within 14 days even if rerefrigerated.[5]

* Dose of atracurium above 0.5 mg/kg is not recommended.
† As originally supplied by the respective manufacturers.
‡ Storage after reconstitution varies with solution. See package insert.

Norcuron®

(vecuronium bromide) for injection

A LOGICAL CHOICE FOR NEUROMUSCULAR BLOCKADE

See following page for brief summary of prescribing information.

Organon

ORGANON INC.
WEST ORANGE
NEW JERSEY 07052

Norcuron®

(vecuronium bromide) for injection

Before prescribing, please consult complete product information, a summary of which follows:

THIS DRUG SHOULD BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS.

CONTRAINDICATIONS: Norcuron® is contraindicated in patients known to have a hypersensitivity to it.

WARNINGS: NORCURON® SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION. TO REDUCE THE POSSIBILITY OF PROLONGED NEUROMUSCULAR BLOCKADE AND OTHER POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING LONG-TERM USE IN THE ICU, NORCURON® OR ANY OTHER NEUROMUSCULAR BLOCKING AGENT SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSES BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH ITS ACTIONS AND WHO ARE FAMILIAR WITH APPROPRIATE PERIPHERAL NERVE STIMULATOR MUSCLE MONITORING TECHNIQUES (see PRECAUTIONS). In patients who are known to have myasthenia gravis or the myasthenic (Eaton-Lambert) syndrome, small doses of Norcuron® may have profound effects. In such patients, a peripheral nerve stimulator and use of a small test dose may be of value in monitoring the response to administration of muscle relaxants.

PRECAUTIONS:

Renal Failure: Norcuron® is well tolerated without clinically significant prolongation of neuromuscular blocking effect in patients with renal failure who have been optimally prepared for surgery by dialysis. Under emergency conditions in anephric patients some prolongation of neuromuscular blockage may occur; therefore, if anephric patients cannot be prepared for non-elective surgery, a lower initial dose of Norcuron® should be considered.

Altered Circulation Time: Conditions associated with slower circulation time in cardiovascular disease, old age, edematous states resulting in increased volume of distribution may contribute to a delay in onset time, therefore dosage should not be increased.

Hepatic Disease: Limited experience in patients with cirrhosis or cholestasis has revealed prolonged recovery time in keeping with the role the liver plays in Norcuron® metabolism and excretion. Data currently available do not permit dosage recommendations in patients with impaired liver function.

Long-term Use in I.C.U.: In the intensive care unit, in rare cases, long-term use of neuromuscular blocking drugs to facilitate mechanical ventilation may be associated with prolonged paralysis and/or skeletal muscle weakness that may be first noted during attempts to wean such patients from the ventilator. Typically, such patients receive other drugs such as broad spectrum antibiotics, narcotics and/or steroids and may have electrolyte imbalance and diseases which lead to electrolyte imbalance, hypoxic episodes of varying duration, acid-base imbalance and extreme debilitation, any of which may enhance the actions of a neuromuscular blocking agent. Additionally, patients immobilized for extended periods frequently develop symptoms consistent with disuse muscle atrophy. The recovery picture may vary from regaining movement and strength in all muscles to initial recovery of movement of the facial and small muscles of the extremities then to the remaining muscles. In rare cases recovery may be over an extended period of time and may even, on occasion, involve rehabilitation. Therefore, when there is a need for long-term mechanical ventilation, the benefits-to-risk ratio of neuromuscular blockade must be considered. Continuous infusion or intermittent bolus dosing to support mechanical ventilation has not been studied sufficiently to support dosage recommendations.

IN THE INTENSIVE CARE UNIT, APPROPRIATE MONITORING, WITH THE USE OF A PERIPHERAL NERVE STIMULATOR TO ASSESS THE DEGREE OF NEUROMUSCULAR BLOCKADE, IS RECOMMENDED TO HELP PRECLUDE POSSIBLE PROLONGATION OF THE BLOCKADE. WHENEVER THE USE OF NORCURON® OR ANY NEUROMUSCULAR BLOCKING AGENT IS CONTEMPLATED IN THE ICU, IT IS RECOMMENDED THAT NEUROMUSCULAR TRANSMISSION BE MONITORED CONTINUOUSLY DURING ADMINISTRATION AND RECOVERY WITH THE HELP OF A NERVE STIMULATOR. ADDITIONAL DOSES OF NORCURON® OR ANY OTHER NEUROMUSCULAR BLOCKING AGENT SHOULD NOT BE GIVEN BEFORE THERE IS A DEFINITE RESPONSE TO T_1 OR TO THE FIRST TWITCH. IF NO RESPONSE IS ELICITED, INFUSION ADMINISTRATION SHOULD BE DISCONTINUED UNTIL A RESPONSE RETURNS.

Severe Obesity or Neuromuscular Disease: Patients with severe obesity or neuromuscular disease may pose airway and/or ventilatory problems requiring special care before, during and after the use of neuromuscular blocking agents such as Norcuron®.

Malignant Hyperthermia: Many drugs used in anesthetic practice are suspected of being capable of triggering a potentially fatal hypermetabolism of skeletal muscle known as malignant hyperthermia. There are insufficient data derived from screening in susceptible animals (swine) to establish whether or not Norcuron® is capable of triggering malignant hyperthermia.

C.N.S.: Norcuron® has no known effect on consciousness, the pain threshold or cerebration. Administration must be accompanied by adequate anesthesia or sedation.

Drug Interactions: Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron® (vecuronium bromide) for injection and its duration of action. If succinylcholine is used before Norcuron®, the administration of Norcuron® should be delayed until the succinylcholine effect shows signs of wearing off. With succinylcholine as the intubating agent, initial doses of 0.04-0.06 mg/kg of Norcuron® may be administered to produce complete neuromuscular block with clinical duration of action of 25-30 minutes. The use of Norcuron® before succinylcholine, in order to attenuate some of the side effects of succinylcholine, has not been sufficiently studied.

Other nondepolarizing neuromuscular blocking agents (pancuronium, d-tubocurarine, metocurine, and gallamine) act in the same fashion as does Norcuron®, therefore these drugs and Norcuron® may manifest an additive effect when used together. There are insufficient data to support concomitant use of Norcuron® and other competitive muscle relaxants in the same patient.

Inhalational Anesthetics: Use of volatile inhalational anesthetics such as enflurane, isoflurane, and halothane with Norcuron® will enhance neuromuscular blockade. Potentiation is most prominent with use of enflurane and isoflurane. With the above agents the initial dose of Norcuron® may be the same as with balanced anesthesia unless the inhalational anesthetic has been administered for a sufficient time at a sufficient dose to have reached clinical equilibrium.

Antibiotics: Parenteral/intraperitoneal administration of high doses of certain antibiotics may intensify or produce neuromuscular block on their own. The following antibiotics have been associated with various degrees of paralysis: aminoglycosides (such as neomycin, streptomycin, kanamycin, gentamicin, and dihydrostreptomycin); tetracyclines; bacitracin; polymyxin B; colistin; and sodium colistimethate. If these or other newly introduced antibiotics are used in conjunction with Norcuron®, unexpected prolongation of neuromuscular block should be considered a possibility.

Other: Experience concerning injection of quinidine during recovery from use of other muscle relaxants suggest that recurrent paralysis may occur. This possibility must also be considered for Norcuron®. Norcuron® induced neuromuscular blockade has been counteracted by alkalosis and enhanced by acidosis in experimental animals (cat). Electrolyte imbalance and diseases which lead to electrolyte imbalance, such as adrenal cortical insufficiency, have been shown to alter neuromuscular blockade. Depending on the nature of the imbalance, either enhancement or inhibition may be expected. Magnesium salts, administered for the management of toxemia of pregnancy, may enhance the neuromuscular blockade.

Drug/laboratory test interactions: None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential or impairment of fertility.

Pregnancy: Pregnancy Category C: Animal reproduction studies have not been conducted with Norcuron®. It is also not known whether Norcuron® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Norcuron® should be given to a pregnant woman only if clearly needed.

Pediatric Use: Infants under 1 year of age but older than 7 weeks, also tested under halothane anesthesia, are moderately more sensitive to Norcuron® on a mg/kg basis than adults and take about 1½ times as long to recover. Information presently available does not permit recommendations for usage in neonates.

ADVERSE REACTIONS: The most frequent adverse reaction to nondepolarizing blocking agents as a class consists of an extension of the drug's pharmacological action beyond the time period needed. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiration insufficiency or apnea.

Inadequate reversal of the neuromuscular blockade is possible with Norcuron® as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate. Little or no increase in intensity of blockade or duration of action of Norcuron® is noted from the use of thiobarbiturates, narcotic analgesics, nitrous oxide, or droperidol. See OVERDOSAGE for discussion of other drugs used in anesthetic practice which also cause respiratory depression.

Prolonged to profound extensions of paralysis and/or muscle weakness as well as muscle atrophy have been reported after long-term use to support mechanical ventilation in the intensive care unit (see PRECAUTIONS).

The administration of Norcuron® has been associated with rare instances of hypersensitivity reactions (bronchospasm, hypotension and/or tachycardia, sometimes associated with acute urticaria or erythema).

OVERDOSAGE: The possibility of iatrogenic overdosage can be minimized by carefully monitoring muscle twitch response to peripheral nerve stimulation.

Excessive doses of Norcuron® produce enhanced pharmacological effects. Residual neuromuscular blockage beyond the time period needed may occur with Norcuron® as with other neuromuscular blockers. This may be manifested by skeletal muscle weakness, decreased respiratory reserve, low tidal volume, or apnea. A peripheral nerve stimulator may be used to assess the degree of residual neuromuscular blockade from other causes of decreased respiratory reserve.

Respiratory depression may be due either wholly or in part to other drugs used during the conduct of general anesthesia such as narcotics, thiobarbiturates and other central nervous system depressants. Under such circumstances, the primary treatment is maintenance of a patent airway and manual or mechanical ventilation until complete recovery of normal respiration is assured. Regonol® (pyridostigmine bromide) injection, neostigmine, or edrophonium, in conjunction with atropine or glycopyrrolate will usually antagonize the skeletal muscle relaxant action of Norcuron®. Satisfactory reversal can be judged by adequacy of skeletal muscle tone and by adequacy of respiration. A peripheral nerve stimulator may also be used to monitor restoration of twitch height. Failure of prompt reversal (within 30 minutes) may occur in the presence of extreme debilitation, carcinomatosis, and with concomitant use of certain broad spectrum antibiotics, or anesthetic agents and other drugs which enhance neuromuscular blockade or cause respiratory depression of their own. Under such circumstances the management is the same as that of prolonged neuromuscular blockade. Ventilation must be supported by artificial means until the patient has resumed control

DOSAGE AND ADMINISTRATION: Before prescribing, please consult complete product information. Norcuron® (vecuronium bromide) for injection is for intravenous use only. This drug should be administered by or under the supervision of experienced clinicians familiar with the use of neuromuscular blocking agents. Dosage must be individualized in each case. The dosage information which follows is derived from studies based upon units of drug per unit of body weight and is intended to serve as a guide only, especially regarding enhancement of neuromuscular blockade of Norcuron® by volatile anesthetics and by prior use of succinylcholine (see PRECAUTIONS/Drug Interactions). Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

To obtain maximum clinical benefits of Norcuron® and to minimize the possibility of overdosage, the monitoring of muscle twitch response to peripheral nerve stimulation is advised.

The recommended initial dose of Norcuron® is 0.08 to 0.10 mg/kg (1.4 to 1.75 times the ED_{90}) given as an intravenous bolus injection. This dose can be expected to produce good or excellent non-emergency intubation conditions in 2.5 to 3 minutes after injection. Under balanced anesthesia, clinically required neuromuscular blockade lasts approximately 25-30 minutes, with recovery to 25% of control achieved approximately 25 to 40 minutes after injection and recovery to 95% of control achieved approximately 45-65 minutes after injection. In the presence of potent inhalation anesthetics, the neuromuscular blocking effect of Norcuron® is enhanced. If Norcuron® is first administered more than 5 minutes after the start of inhalation agent or when steady state has been achieved, the initial Norcuron® dose may be reduced by approximately 15%, i.e., 0.060 to 0.085 mg/kg.

Prior administration of succinylcholine may enhance the neuromuscular blocking effect and duration of action of Norcuron®. If intubation is performed using succinylcholine, a reduction of initial dose of Norcuron® to 0.04-0.06 mg/kg with inhalation anesthesia and 0.05-0.06 mg/kg with balanced anesthesia may be required.

During prolonged surgical procedures, maintenance doses of 0.010 to 0.015 mg/kg of Norcuron® are recommended; after the initial Norcuron® injection, the first maintenance dose will generally be required within 25 to 40 minutes. However, clinical criteria should be used to determine the need for maintenance doses. Since Norcuron® lacks clinically important cumulative effects, subsequent maintenance doses, if required, may be administered at relatively regular intervals for each patient, ranging approximately from 12 to 15 minutes under balanced anesthesia, slightly longer under inhalation agents. (If less frequent administration is desired, higher maintenance doses may be administered.)

Should there be reason for the selection of larger doses in individual patients, initial doses ranging from 0.15 mg/kg up to 0.28 mg/kg have been administered during surgery under halothane anesthesia without ill effects to the cardiovascular system being noted as long as ventilation is properly maintained.

Use by Continuous Infusion: After an intubating dose of 80-100 µg/kg, a continuous infusion of 1 µg/kg/min can be initiated approximately 20-40 min later. Infusion of Norcuron® should be initiated only after early evidence of spontaneous recovery from the bolus dose. Long-term intravenous infusion to support mechanical ventilation in the intensive care unit has not been studied sufficiently to support dosage recommendations (see PRECAUTIONS).

The infusion of Norcuron® should be individualized for each patient. The rate of administration should be adjusted according to the patient's twitch response as determined by peripheral nerve stimulation. An initial rate of 1 µg/kg/min is recommended, with the rate of the infusion adjusted thereafter to maintain a 90% suppression of twitch response. Average infusion rates may range from 0.8 to 1.2 µg/kg/min.

Inhalation anesthetics, particularly enflurane and isoflurane may enhance the neuromuscular blocking action of non-depolarizing muscle relaxants. In the presence of steady-state concentrations of enflurane or isoflurane, it may be necessary to reduce the rate of infusion 25-60 percent, 45-60 min after the intubating dose. Under halothane anesthesia it may not be necessary to reduce the rate of infusion.

Spontaneous recovery and reversal of neuromuscular blockade following discontinuation of Norcuron® infusion may be expected to proceed at rates comparable to that following a single bolus dose.

Infusion solutions of Norcuron® can be prepared by mixing Norcuron® with an appropriate infusion solution such as 5% glucose in water, 0.9% NaCl, 5% glucose in saline, or Lactated Ringers. Unused portions of infusion solutions should be discarded.

Infusion rates of Norcuron® can be individualized for each patient using the following table:

Drug Delivery Rate (µg/kg/min)	Infusion Delivery Rate (mL/kg/min)	
	0.1 mg/mL*	0.2 mg/mL†
0.7	0.007	0.0035
0.8	0.008	0.0040
0.9	0.009	0.0045
1.0	0.010	0.0050
1.1	0.011	0.0055
1.2	0.012	0.0060
1.3	0.013	0.0065

*10 mg of Norcuron® in 100 mL solution †20 mg of Norcuron® in 100 mL solution

The following table is a guideline for mL/min delivery for a solution of 0.1 mg/mL (10 mg in 100 mL) with an infusion pump.

NORCURON® INFUSION RATE – mL/MIN

Amount of Drug µg/kg/min	Patient Weight – kg						
	40	50	60	70	80	90	100
0.7	0.28	0.35	0.42	0.49	0.56	0.63	0.70
0.8	0.32	0.40	0.48	0.56	0.64	0.72	0.80
0.9	0.36	0.45	0.54	0.63	0.72	0.81	0.90
1.0	0.40	0.50	0.60	0.70	0.80	0.90	1.00
1.1	0.44	0.55	0.66	0.77	0.88	0.99	1.10
1.2	0.48	0.60	0.72	0.84	0.96	1.08	1.20
1.3	0.52	0.65	0.78	0.91	1.04	1.17	1.30

NOTE: If a concentration of 0.2 mg/mL is used (20 mg in 100 mL), the rate should be decreased by one-half.

Dosage in Children: Older children (10 to 17 years of age) have approximately the same dosage requirements (mg/kg) as adults and may be managed the same way. Younger children (1 to 10 years of age) may require a slightly higher initial dose and may also require supplementation slightly more often than adults. Infants under one year of age but older than 7 weeks are moderately more sensitive to Norcuron® on a mg/kg basis than adults and take about 1½ times as long to recover. See also subsection of PRECAUTIONS titled Pediatric Use. Information presently available does not permit recommendation on usage in neonates (see PRECAUTIONS). There are insufficient data concerning continuous infusion of vecuronium in children, therefore, no dosing recommendation can be made.

COMPATIBILITY: Norcuron® is compatible in solution with:

0.9% NaCl solution   Sterile water for injection   Lactated Ringers
5% glucose in water   5% glucose in saline

Use within 24 hours of mixing with the above solutions.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

HOW SUPPLIED:

10 mL vials (10 mg vecuronium bromide) and 10 mL prefilled syringes of diluent (bacteriostatic water for injection, USP).
22 g 1¼" needle.   Boxes of 10   NDC No. 0052-0441-60
10 mL vials (10 mg vecuronium bromide) and 10 mL vials of diluent (bacteriostatic water for injection, USP).
Boxes of 10   NDC No. 0052-0441-17
10 mL vials (10 mg vecuronium bromide) only; DILUENT NOT SUPPLIED.   Boxes of 10   NDC No. 0052-0441-15
20 mL vials (20 mg vecuronium bromide) only; DILUENT NOT SUPPLIED.   Boxes of 10   NDC No. 0052-0442-46

STORAGE: 15°-30°C (59°-86°F). Protect from light.

AFTER RECONSTITUTION:

- When reconstituted with supplied bacteriostatic water for injection: CONTAINS BENZYL ALCHOHOL, WHICH IS NOT INTENDED FOR USE IN NEWBORNS. Use within 5 days. May be stored at room temperature or refrigerated.
- When reconstituted with sterile water for injection or other compatible I.V. solutions: Refrigerate vial. Use within 24 hours. Single use only. Discard unused portion.

Caution: Federal law prohibits dispensing without prescription.

References

1. Gallo JA, Cork RC, Puchi P. Comparison of effects of atracurium and vecuronium in cardiac surgical patients. *Anesth Analg.* 1988;67:161-165. 2. Basta SJ, Savarese JJ, Ali HH, et al. Vecuronium does not alter serum histamine within clinical dose range. *Anesthesiol.* 1983;58(3):A273. 3. Norcuron® (vecuronium bromide) for injection package insert. 4. Kaufman JA, Dubois MY, Chen JC, Lea D. Pharacodynamic effects of vecuronium: A dose response study. *J Clin Anesth.* 1989;1(6):434-439. 5. Tracrium* Injection (atracurium besylate) package insert. 6. Scott RPF, Savarese JJ, Basta SJ, et al. Atracurium: Clinical strategies for preventing histamine release and attenuating the haemodynamic response. *Br J Anaesth.* 1985;57:550-553.

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T. H. Seldon Memorial Lecture, Sunday, March 21, 1993, 11 AM
"Relationships Between Anesthesiology and Industry: A Mixed Blessing"
Lawrence J. Saidman, MD

REVIEW COURSE LECTURES:

PG Barash, MD	—Preoperative Risk Assessment
G Bashein, MD	—New Ultrasound Technology in Anesthesiology
JL Benumof, MD	—Management Algorithm for the Difficult Airway
AR Brown, MB, ChB	—What's New in Regional Anesthesia
RA Caplan, MD	—Closed Claim Studies—Relevance to the Anesthesiologist
N Ellison, MD	—Alternatives to Allogenic (Homologous) Blood
FM Ferrante, MD	—Acute Pain Management
TJ Gal, MD	—Preoperative Preparation of the Thoracic Surgery Patient
E Geller, MD	—Benzodiazepines and Their Antagonists in Anesthesia
SC Hall, MD	—What's New in Pediatric Anesthesia
M Maze, MD	—Alpha$_2$ Agonists in Anesthesia: The How, Why and When . . .
LN Milde, MD	—What's New in Neuroanesthesia
RD Miller, MD	—Use of Muscle Relaxants in Non-Operating Room Locations
RG Pearl, MD, PhD	—What's New in Intensive Care
L Priano, MD, PhD	—Anesthesia for Vascular Surgery—Patient Assessment and Anesthetic Delivery
DS Prough, MD	—Management of Cerebral Ischemia
JG Reves, MD	—What's New in Cardiac Anesthesia
MF Roizen, MD	—Outcome Studies: How Should They Affect My Practice?
JJ Savarese, MD	—Reversal of Neuromuscular Blockade—More Controversial Than Ever?
RN Sladen, MD	—Temperature Regulation in the OR
S Slogoff, MD	—Monitoring for Myocardial Ischemia—How, When, Why Bother?
TH Stanley, MD	—Anesthesia with Narcotics—Does Everyone Need 2 cc's of Fentanyl?
RK Stoelting, MD	—Understanding Allergic Reactions
JH Tinker, MD	—CQI—Continuous Quality Improvement
H Van Aken, MD, PhD	—Deliberate Hypotension
PF White, PhD, MD	—Short Acting Drugs—Do They Make a Difference?

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Ask the Expert: Ambulatory Anesthesia
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Deep Hypothermic Circulatory Arrest
Regional Blocks: How to Do Them
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Ask the Expert: Neuroanesthesia
TEE: For the Neophyte
Comparative Medical Economics—Canada, Europe, Japan
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FEES—*IARS Members:* $325 ($350 on site); *Non-Members:* $500 ($525 on site); *IARS Educational Members:* No Fee; *Non-Member Residents:* $50 (with certification). Registration opens at 1 PM on Friday, March 19. Scientific sessions are scheduled from 8:30 AM to 5 PM on Saturday, Sunday, and Monday and from 8:30 AM to noon on Tuesday.

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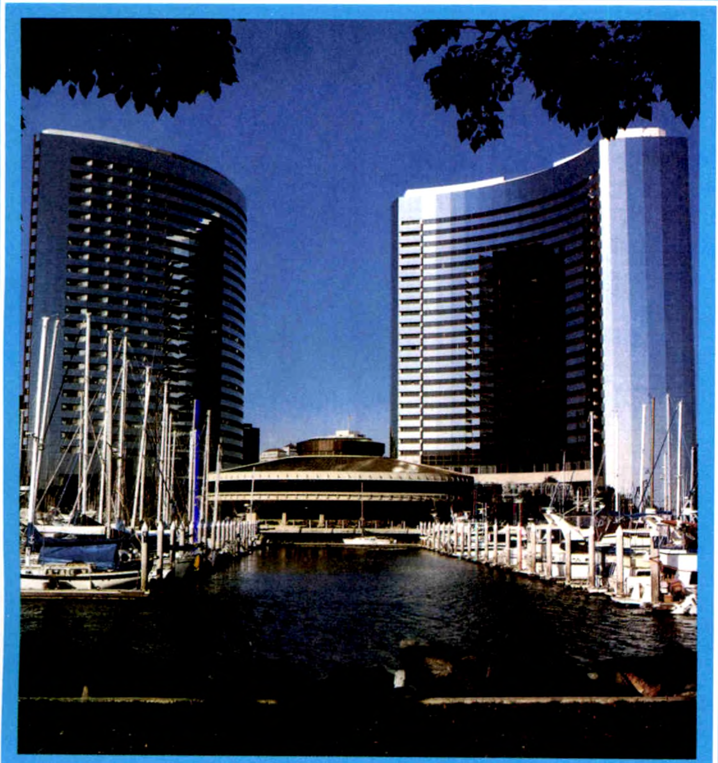

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MARCH 19 -23, 1993

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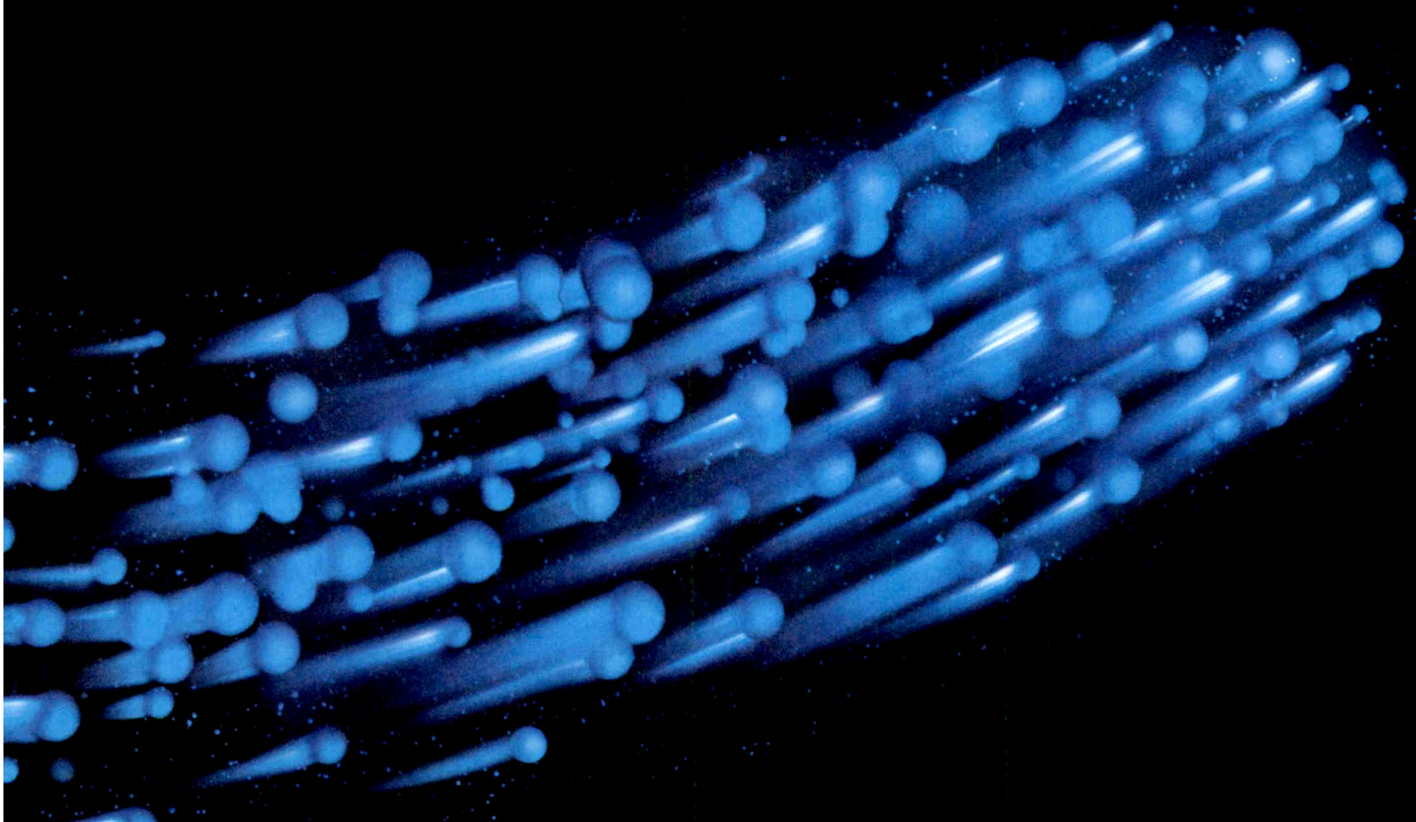

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Books for review should be sent directly to Norig Ellison, MD, Book Review Editor, Department of Anesthesia, University of Pennsylvania, Philadelphia, PA 19104.

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1993

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Within the general field of perioperative trauma anesthesia and critical care, including basic science or clinical research, clinical management, education, or administration.

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  - —Post-Op Critical Care: PACU/ICU
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  - —Applications must be accompanied by a budget list, copies of previously published material in the area, and any supporting documents to assess project viability
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Technical Report

Real time nitrogen monitoring: a unique parameter in patient care.

Summary.

Real time nitrogen monitoring provides unique clinical information. It allows differentiation and diagnosis of significant events - events which otherwise would be difficult to confirm. Overall, knowledge of circuit nitrogen concentrations can greatly enhance patient safety.

Detecting Venous Air Emboli.

Venous air emboli (VAE) occur when air enters the circulation through a lacerated vein in which venous pressure is below atmospheric pressure.[1]

Embolic events have been described in spinal fusions,[2] neuro procedures, organ transplantation[3] and orthopedic surgery.[4]

Air embolism involves air passing through the right heart and traversing the alveolar-capillary membrane. It can be measured as an increase in end-tidal nitrogen (EtN_2). Catastrophic VAE occur when large amounts of air enter the right heart creating an air lock.

Monitoring EtN_2 is a superior method for confirming the diagnosis of VAE.[5] Blood loss or sudden reductions in cardiac output can decrease $EtCO_2$ in the absence of VAE. VAE remain the only cause for sudden EtN_2 increase.[6]

Verifying Adequate Denitrogenation.

Preoxygenation prior to general anesthesia is used to prevent hypoxemia. The time required to preoxygenate a patient adequately can vary widely - it can be up to 10 minutes.

This is a special concern for babies and infants due to their increased metabolic rate; for patients with lung disease;[7] and for the obese, who may have less reserve due to reduced lung capacity.

The ability to assess adequacy of denitrogenation is paramount to patient safety. Rather than watching for increasing SpO_2, the key is observing wash-out of N_2 from the lungs.

Monitoring is the only way to be sure.

Monitoring Anesthesia Circuit Integrity.

Room air can be entrained into the anesthesia circuit. Entrained air contaminates the gas mixture with N_2 and can therefore be detected. Entrained air dilutes the mixture the patient is receiving, compromises the readings of monitoring devices and can thereby mask significant physiological changes.

Monitoring N_2 is the fastest and most reliable way to detect leaks.[8]

Detecting Nitrogen Accumulation.

In spite of high initial gas flows and denitrogenation procedures, excreted N_2 builds up during both closed circuit and low-flow anesthesia. N_2 levels as high as 15% have been reported during closed circuit anesthesia.[9]

N_2 accumulation decreases O_2 and N_2O concentrations and affects the depth of anesthesia. Thus, N_2 monitoring rather than simple maintenance of circuit volume is an important criterion for closed circuit anesthesia.[10]

More Information.

Please contact your Ohmeda representative if you would like more background on the advantages of nitrogen monitoring.

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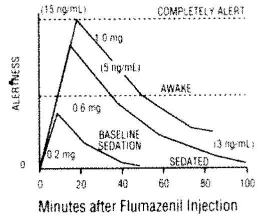
DESCRIPTION: MAZICON™ (flumazenil/Roche) is a benzodiazepine receptor antagonist. Chemically, flumazenil is ethyl 8-fluoro-5,6-dihydro-5-methyl-6-oxo-4H-imidazo[1,5-a](1,4) benzodiazepine-3-carboxylate. Flumazenil has an imidazobenzodiazepine structure, a calculated molecular weight of 303.3.
Flumazenil is a white to off-white crystalline compound with an octanol:buffer partition coefficient of 14 to 1 at pH 7.4. It is insoluble in water but slightly soluble in acidic aqueous solutions. MAZICON is available as a sterile parenteral dosage form for intravenous administration. Each mL contains 0.1 mg of flumazenil compounded with 1.8 mg of methylparaben, 0.2 mg of propylparaben, 0.9% sodium chloride, 0.01% edetate disodium, and 0.01% acetic acid; the pH is adjusted to approximately 4 with hydrochloric acid and/or, if necessary, sodium hydroxide.

CLINICAL PHARMACOLOGY: Flumazenil, an imidazobenzodiazepine derivative, antagonizes the actions of benzodiazepines on the central nervous system. Flumazenil competitively inhibits the activity at the benzodiazepine recognition site on the GABA/benzodiazepine receptor complex. Flumazenil is a weak partial agonist in some animal models of activity, but has little or no agonist activity in man.
Flumazenil does not antagonize the central nervous system effects of drugs affecting GABA-ergic neurons by means other than the benzodiazepine receptor (including ethanol, barbiturates, or general anesthetics) and does not reverse the effects of opioids.
PHARMACODYNAMICS: Intravenous MAZICON has been shown to antagonize sedation, impairment of recall and psychomotor impairment produced by benzodiazepines in healthy human volunteers.
The duration and degree of reversal of benzodiazepine effects are related to the dose and plasma concentrations of flumazenil as shown in the following data from a study in normal volunteers.

Magnitude and Duration of Reversal of Sedation as a Function of Flumazenil Dose*
Flumazenil doses of 0.2, 0.6 & 1.0 mg
(blood level in ng/mL)



*Sedation produced by midazolam infusion at a rate of 0.06 - 0.20 mg/kg/hr in healthy volunteers

Generally, doses of approximately 0.1 to 0.2 mg (corresponding to peak plasma levels of 3 to 6 ng/mL) produce partial antagonism, whereas higher doses of 0.4 to 1.0 mg (peak plasma levels of 12 to 28 ng/mL) usually produce complete antagonism in patients who have received the usual sedating doses of benzodiazepines. The onset of reversal is usually evident within 1 to 2 minutes after the injection is completed. Eighty percent response will be reached within 3 minutes, with the peak effect occurring at 6 to 10 minutes. The duration and degree of reversal are related to the plasma concentration of the sedating benzodiazepine as well as the dose of MAZICON given.
In healthy volunteers, MAZICON did not alter intraocular pressure when given alone and reversed the decrease in intraocular pressure seen after administration of midazolam.
PHARMACOKINETICS: After IV administration, plasma concentrations of flumazenil follow a two compartment open pharmacokinetic model with an initial distribution half-life of 7 to 15 minutes and a terminal half-life of 41 to 79 minutes. Peak concentrations of flumazenil are proportional to dose, with an apparent initial volume of distribution of 0.5 L/kg. After redistribution the apparent volume of distribution (V_{SS}) ranges from 0.77 to 1.60 L/kg. Protein binding is approximately 50% and the drug shows no preferential partitioning into red blood cells. Flumazenil is a highly extracted drug. Clearance of flumazenil occurs primarily by hepatic metabolism and is dependent on hepatic blood flow. In pharmacokinetic studies of normal volunteers, total clearance ranges from 0.7 to 1.3 L/hr/kg, with less than 1% of the administered dose eliminated unchanged in the urine. The major metabolites of flumazenil identified in urine are the de-ethylated free acid and its glucuronide conjugate. In preclinical studies there was no evidence of pharmacologic activity exhibited by the de-ethylated free acid. Elimination of radiolabelled drug is essentially complete within 72 hours, with 90% to 95% of the radioactivity appearing in urine and 5% to 10% in the feces.

Pharmacokinetic Parameters Following a 5-minute infusion of a total of 1.0 mg of MAZICON Mean (Coefficient of variation, Range)

C_{max} (ng/mL)	24 (38%, 11-43)
AUC (ng•hr/mL)	15 (22%, 10-22)
V_{ss} (L/kg)	1 (24%, 0.8-1.6)
Cl (L/hr/kg)	1 (20%, 0.7-1.4)
Half-life (min)	54 (21%, 41-79)

The pharmacokinetics of flumazenil are not significantly affected by gender, age, renal failure (creatinine clearance <10 mL/min), or hemodialysis beginning 1 hour after drug administration. Mean total clearance is decreased to 40% to 60% of normal in patients with moderate liver dysfunction and to 25% of normal in patients with severe liver dysfunction compared with age-matched healthy subjects. This results in a prolongation of the half-life from 0.8 hours in healthy subjects to 1.3 hours in patients with moderate hepatic impairment and 2.4 hours in severely impaired patients. Ingestion of food during an intravenous infusion of the drug results in a 50% increase in clearance, most likely due to the increased hepatic blood flow that accompanies a meal. The pharmacokinetic profile of flumazenil is unaltered in the presence of benzodiazepine agonists and the kinetic profiles of those benzodiazepines are unaltered by flumazenil.

CLINICAL TRIALS: MAZICON has been administered to reverse the effects of benzodiazepines in conscious sedation, general anesthesia, and the management of suspected benzodiazepine overdose.
CONSCIOUS SEDATION: MAZICON was studied in four trials in 970 patients who received an average of 30 mg diazepam or 10 mg midazolam for sedation (with or without a narcotic) in conjunction with both inpatient and outpatient diagnostic or surgical procedures. MAZICON was effective in reversing the sedating and psychomotor effects of the benzodiazepine, however, amnesia was less completely and less consistently reversed. In these studies, MAZICON was administered as an initial dose of 0.4 mg I.V. (two doses of 0.2 mg) with additional 0.2 mg doses as needed to achieve complete awakening, up to a maximum total dose of 1.0 mg. Seventy-eight percent of patients receiving flumazenil responded by becoming completely alert. Of those patients, approximately half responded to doses of 0.4 to 0.6 mg, while the other half responded to doses of 0.8 to 1.0 mg. Adverse effects were infrequent in patients who received 1 mg of MAZICON or less, although injection site pain, agitation and anxiety did occur. Reversal of sedation was not associated with any increase in the frequency of inadequate analgesia or increase in narcotic demand in these studies. While most patients remained alert throughout the 3 hour post-procedure observation period, resedation was observed to occur in 3% to 9% of the patients, and was most common in patients who had received high doses of benzodiazepine. (See PRECAUTIONS.)
GENERAL ANESTHESIA: MAZICON was studied in four trials in 644 patients who received midazolam as an induction and/or maintenance agent in both balanced and inhalational anesthesia. Midazolam was generally administered in doses ranging from 5 to 80 mg, alone and/or in conjunction with muscle relaxants, nitrous oxide, regional or local anesthetics, narcotics and/or inhalational anesthetics. Flumazenil was given as an initial dose of 0.2 mg IV, with additional 0.2 mg doses as needed to reach a complete response, up to a maximum total dose of 1.0 mg. These doses were effective in reversing sedation and restoring psychomotor function, but did not completely restore memory as tested by picture recall. MAZICON was not as effective in the reversal of sedation in patients who had received multiple anesthetic agents in addition to benzodiazepines.
Eighty-one percent of patients sedated with midazolam responded to flumazenil by becoming completely alert or just slightly drowsy. Of those patients, 36% responded to doses of 0.4 to 0.6 mg, while 64% responded to doses of 0.8 to 1.0 mg.
Resedation in patients who responded to MAZICON occurred in 10% to 15% of patients studied and was more common with larger doses of midazolam (>20 mg), long procedures (>60 minutes) and use of neuromuscular blocking agents. (See PRECAUTIONS.)
MANAGEMENT OF SUSPECTED BENZODIAZEPINE OVERDOSE: MAZICON was studied in two trials in 497 patients who were presumed to have taken an overdose of a benzodiazepine, either alone or in combination with a variety of other agents. In these trials, 299 patients were proven to have taken a benzodiazepine as part of the overdose, and 80% of the 148 who received MAZICON responded by an improvement in level of consciousness. Of the patients who responded to flumazenil, 75% responded to a total dose of 1.0 to 3.0 mg. Reversal of sedation was associated with an increased frequency of symptoms of CNS excitation. Of the

patients treated with flumazenil, 1% to 3% were treated for agitation or anxiety. Serious side effects were uncommon, but six seizures were observed in 446 patients treated with flumazenil in these studies. Four of these 6 patients had ingested a large dose of cyclic antidepressants, which increased the risk of seizures. (See WARNINGS.)

INDIVIDUALIZATION OF DOSAGE: GENERAL PRINCIPLES: The serious adverse effects of MAZICON are related to the reversal of benzodiazepine effects. Using more than the minimally effective dose of MAZICON is tolerated by most patients but may complicate the management of patients who are physically dependent on benzodiazepines or patients who are depending on benzodiazepines for therapeutic effect (such as suppression of seizures in cyclic antidepressant overdose).
In high-risk patients, it is important to administer the smallest amount of MAZICON that is effective. The 1-minute wait between individual doses in the dose-titration recommended for general clinical populations may be too short for high risk patients. This is because it takes 6 to 10 minutes for any single dose of flumazenil to reach full effects. Practitioners should slow the rate of administration of MAZICON administered to high risk patients as recommended below.
ANESTHESIA AND CONSCIOUS SEDATION: MAZICON is well tolerated at the recommended doses in individuals who have no tolerance to (or dependence on) benzodiazepines. The recommended dosages and titration rates in anesthesia and conscious sedation (0.2 to 1.0 mg given at 0.2 mg/min) are well tolerated in patients receiving the drug for reversal of a single benzodiazepine exposure in most clinical settings (see Adverse Events). The major risk will be resedation because the duration of effect of a long-acting (or large dose of a short-acting) benzodiazepine may exceed that of MAZICON. Resedation may be treated by giving a repeat dose at no less than 20-minute intervals. For repeat treatment, no more than 1.0 mg (at 0.2 mg/min doses) should be given at any one time and no more than 3.0 mg should be given in any one hour.
OVERDOSE PATIENTS: The risk of confusion, agitation, emotional lability and perceptual distortion with the doses recommended in patients with benzodiazepine overdose (3 to 5 mg administered as 0.5 mg/min) may be greater than that expected with lower doses and slower administration. The recommended doses represent a compromise between a desirable slow awakening and the need for prompt response and a persistent effect in the overdose situation. If circumstances permit, the physician may elect to use the 0.2 mg/minute titration rate to slowly awaken the patient over 5 to 10 minutes, which may help to reduce signs and symptoms on emergence.
MAZICON has no effect in cases where benzodiazepines are not responsible for sedation. Once doses of 3 to 5 mg have been reached without clinical response, additional MAZICON is likely to have no effect.
PATIENTS TOLERANT TO BENZODIAZEPINES: MAZICON may cause benzodiazepine withdrawal symptoms in individuals who have been taking benzodiazepines long enough to have some degree of tolerance. Patients who had been taking benzodiazepines prior to entry into the MAZICON trials who were given flumazenil in doses over 1 mg experienced withdrawal-like events 2 to 5 times more frequently than patients who received less than 1 mg.
In patients who may have tolerance to benzodiazepines, as indicated by clinical history or by the need for larger than usual doses of benzodiazepine, slower titration rates of 0.1 mg/min and lower total doses may help reduce the frequency of emergent confusion and agitation. In such cases special care must be taken to monitor the patients for resedation because of the lower doses of MAZICON used.
PATIENTS PHYSICALLY DEPENDENT ON BENZODIAZEPINES: MAZICON is known to precipitate withdrawal seizures in patients who are physically dependent on benzodiazepines, even if such dependence was established in a relatively few days of high dose sedation in Intensive Care Unit environments. The risk of either seizures or resedation in such cases is high and patients have experienced seizures before regaining consciousness. MAZICON should be used in such settings with extreme caution, since the use of flumazenil in this situation has not been studied and no information as to dose and rate of titration is available. MAZICON should be used in such patients only if the potential benefits of using the drug outweigh the risks of precipitated seizures. Physicians are directed to the scientific literature for the most current information in this area.

INDICATIONS AND USAGE: MAZICON is indicated for the complete or partial reversal of the sedative effects of benzodiazepines in cases where general anesthesia has been induced and/or maintained with benzodiazepines, where sedation has been produced with benzodiazepines for diagnostic and therapeutic procedures, and for the management of benzodiazepine overdose.

CONTRAINDICATIONS: MAZICON is contraindicated:

- in patients with a known hypersensitivity to flumazenil or to benzodiazepines.
- in patients who have been given a benzodiazepine for control of a potentially life-threatening condition (*e.g.* control of intracranial pressure or status epilepticus).
- in patients who are showing signs of serious cyclic antidepressant overdose. (See WARNINGS.)

WARNINGS:

THE USE OF MAZICON HAS BEEN ASSOCIATED WITH THE OCCURRENCE OF SEIZURES.
THESE ARE MOST FREQUENT IN PATIENTS WHO HAVE BEEN ON BENZODIAZEPINES FOR LONG-TERM SEDATION OR IN OVERDOSE CASES WHERE PATIENTS ARE SHOWING SIGNS OF SERIOUS CYCLIC ANTIDEPRESSANT OVERDOSE.
PRACTITIONERS SHOULD INDIVIDUALIZE THE DOSAGE OF MAZICON AND BE PREPARED TO MANAGE SEIZURES.

Risk of Seizures: The reversal of benzodiazepine effects may be associated with the onset of seizures in certain high-risk populations. Possible risk factors for seizures include: concurrent major sedative-hypnotic drug withdrawal, recent therapy with repeated doses of parenteral benzodiazepines, myoclonic jerking or seizure activity prior to flumazenil administration in overdose cases, or concurrent cyclic antidepressant poisoning.
MAZICON is not recommended in cases of serious cyclic antidepressant poisoning, as manifested by motor abnormalities (twitching, rigidity, focal seizure), dysrhythmia (wide QRS, ventricular dysrhythmia, heart block), anticholinergic signs (mydriasis, dry mucosa, hypo-peristalsis), and cardiovascular collapse at presentation. In such cases MAZICON should be withheld and the patient should be allowed to remain sedated (with ventilatory and circulatory support as needed) until the signs of antidepressant toxicity have subsided. Treatment with MAZICON has no known benefit to the seriously ill mixed-overdose patient other than reversing sedation and should not be used in cases where seizures (from any cause) are likely.
Most convulsions associated with flumazenil administration require treatment and have been successfully managed with benzodiazepines, phenytoin or barbiturates. Because of the presence of flumazenil, higher than usual doses of benzodiazepines may be required.

HYPOVENTILATION: Patients who have received MAZICON for the reversal of benzodiazepine effects (after conscious sedation or general anesthesia) should be monitored for resedation, respiratory depression, or other residual benzodiazepine effects for an appropriate period (up to 120 minutes) based on the dose and duration of effect of the benzodiazepine employed.
This is because MAZICON has not been established as an effective treatment for hypoventilation due to benzodiazepine administration. The availability of flumazenil does not diminish the need for prompt detection of hypoventilation and the ability to effectively intervene by establishing an airway and assisting ventilation.
MAZICON may not fully reverse postoperative airway problems or ventilatory insufficiency induced by benzodiazepines. In addition, even if MAZICON is initially effective, such problems may recur because the effects of MAZICON wear off before the effects of many benzodiazepines.
Overdose cases should always be monitored for resedation until the patients are stable and resedation is unlikely.

PRECAUTIONS: RETURN OF SEDATION: MAZICON may be expected to improve the alertness of patients recovering from a procedure involving sedation or anesthesia with benzodiazepines, but should not be substituted for an adequate period of post-procedure monitoring. The availability of MAZICON does not reduce the risks associated with the use of large doses of benzodiazepines for sedation.
Patients should be monitored for resedation, respiratory depression (see WARNINGS), or other persistent or recurrent agonist effects for an adequate period of time after administration of MAZICON.
Resedation is least likely in cases where MAZICON is administered to reverse a low dose of a short-acting benzodiazepine (<10 mg midazolam). It is most likely in cases where a large single or cumulative dose of a benzodiazepine has been given in the course of a long procedure along with neuromuscular blocking agents and multiple anesthetic agents.
Profound resedation was observed in 1% to 3% of patients in the clinical studies. In clinical situations where resedation must be prevented, physicians may wish to repeat the initial dose (up to 1 mg of MAZICON given at 0.2 mg/min) at 30 minutes and possibly again at 60 minutes. This dosage schedule, although not studied in clinical trials, was effective in preventing resedation in a pharmacologic study in normal volunteers.
USE IN THE ICU: MAZICON should be used with caution in the Intensive Care Unit because of the increased risk of unrecognized benzodiazepine dependence in such settings. MAZICON may produce convulsions in patients physically dependent on benzodiazepines. (See INDIVIDUALIZATION OF DOSAGE AND WARNINGS.)
Administration of MAZICON to diagnose benzodiazepine-induced sedation in the Intensive Care Unit is not recommended due to the risk of adverse events as described above. In addition, the prognostic significance of a patient's failure to respond to flumazenil in cases confounded by metabolic disorder, traumatic injury, drugs other than benzodiazepines, or any other reasons not associated with benzodiazepine receptor occupancy is not known.

USE IN OVERDOSE: MAZICON is intended as an adjunct to, not as a substitute for, proper management of airway, assisted breathing, circulatory access and support, internal decontamination by lavage and charcoal, and adequate clinical evaluation.

Necessary measures should be instituted to secure airway, ventilation and intravenous access prior to administering flumazenil. Upon arousal patients may attempt to withdraw endotracheal tubes and/or intravenous lines as the result of confusion and agitation following awakening.

HEAD INJURY: MAZICON should be used with caution in patients with head injury as it may be capable of precipitating convulsions or altering cerebral blood flow in patients receiving benzodiazepines. It should be used only by practitioners prepared to manage such complications should they occur.

USE WITH NEUROMUSCULAR BLOCKING AGENTS: MAZICON should not be used until the effects of neuromuscular blockade have been fully reversed.

USE IN PSYCHIATRIC PATIENTS: MAZICON has been reported to provoke panic attacks in patients with a history of panic disorder.

PAIN ON INJECTION: To minimize the likelihood of pain or inflammation at the injection site, MAZICON should be administered through a freely flowing intravenous infusion into a large vein. Local irritation may occur following extravasation into perivascular tissues.

USE IN RESPIRATORY DISEASE: The primary treatment of patients with serious lung disease who experience serious respiratory depression due to benzodiazepines should be appropriate ventilatory support (See PRECAUTIONS) rather than the administration of MAZICON. Flumazenil is capable of partially reversing benzodiazepine-induced alterations in ventilatory drive in healthy volunteers, but has not been shown to be clinically effective.

USE IN CARDIOVASCULAR DISEASE: MAZICON did not increase the work of the heart when used to reverse benzodiazepines in cardiac patients when given at a rate of 0.1 mg/min in total doses of less than 0.5 mg in studies reported in the clinical literature. Flumazenil alone had no significant effects on cardiovascular parameters when administered to patients with stable ischemic heart disease.

USE IN LIVER DISEASE: The clearance of MAZICON is reduced to 40% to 60% of normal in patients with mild to moderate hepatic disease and to 25% of normal in patients with severe hepatic dysfunction. (See PHARMACOKINETICS.) While the dose of flumazenil used for initial reversal of benzodiazepine effects is not affected, repeat doses of the drug in liver disease should be reduced in size or frequency.

USE IN DRUG AND ALCOHOL DEPENDENT PATIENTS: MAZICON should be used with caution in patients with alcoholism and other drug dependencies due to the increased frequency of benzodiazepine tolerance and dependence observed in these patient populations.

MAZICON is not recommended either as a treatment for benzodiazepine dependence or for the management of protracted benzodiazepine abstinence syndromes, as such use has not been studied.

The administration of flumazenil can precipitate benzodiazepine withdrawal in animals and man. This has been seen in healthy volunteers treated with therapeutic doses of oral lorazepam for up to 2 weeks who exhibited effects such as hot flushes, agitation and tremor when treated with cumulative doses of up to 3 mg doses of flumazenil.

Similar adverse experiences suggestive of flumazenil precipitation of benzodiazepine withdrawal have occurred in some patients in clinical trials. Such patients had a short-lived syndrome characterized by dizziness, mild confusion, emotional lability, agitation (with signs and symptoms of anxiety), and mild sensory distortions. This response was dose-related, most common at doses above 1 mg, rarely required treatment other than reassurance and was usually short lived. When required (5 to 10 cases), these patients were successfully treated with usual doses of a barbiturate, a benzodiazepine, or other sedative drug.

Practitioners should assume that flumazenil administration may trigger dose-dependent withdrawal syndromes in patients with established physical dependence on benzodiazepines and may complicate the management of withdrawal syndromes for alcohol, barbiturates and cross-tolerant sedatives.

DRUG INTERACTIONS: Interaction with central nervous system depressants other than benzodiazepines has not been specifically studied; however, no deleterious interactions were seen when MAZICON was administered after narcotics, inhalational anesthetics, muscle relaxants and muscle relaxant antagonists administered in conjunction with sedation or anesthesia.

Particular caution is necessary when using MAZICON in cases of mixed drug overdosage since the toxic effects (such as convulsions and cardiac dysrhythmias) of other drugs taken in overdose (especially cyclic antidepressants) may emerge with the reversal of the benzodiazepine effect by flumazenil. (See WARNINGS.)

The pharmacokinetics of benzodiazepines are unaltered in the presence of flumazenil.

USE IN AMBULATORY PATIENTS: The effects of MAZICON may wear off before a long-acting benzodiazepine is completely cleared from the body. In general, if a patient shows no signs of sedation within 2 hours after a 1.0 mg dose of flumazenil, serious resedation at a later time is unlikely. An adequate period of observation must be provided for any patient in whom either long-acting benzodiazepines (such as diazepam) or large doses of short-acting benzodiazepines (such as >10 mg of midazolam) have been used. (See INDIVIDUALIZATION OF DOSAGE.)

Because of the increased risk of adverse reactions in patients who have been taking benzodiazepines on a regular basis, it is particularly important that physicians query carefully about benzodiazepine, alcohol and sedative use as part of the history prior to any procedure in which the use of MAZICON is planned. (See DRUG AND ALCOHOL DEPENDENT PATIENTS.)

INFORMATION FOR PATIENTS: MAZICON does not consistently reverse amnesia. Patients cannot be expected to remember information told to them in the post-procedure period and instructions given to patients should be reinforced in writing or given to a responsible family member. Physicians are advised to discuss with their patients, both before surgery and at discharge, that although the patient may feel alert at the time of discharge, the effects of the benzodiazepine may recur. As a result, the patient should be instructed, preferably in writing, that their memory and judgment may be impaired and specifically advised:

1. Not to engage in any activities requiring complete alertness, and not to operate hazardous machinery or a motor vehicle until at least 18 to 24 hours after discharge, and it is certain no residual sedative effects of the benzodiazepine remain.
2. Not to take any alcohol or non-prescription drugs for 18 to 24 hours after flumazenil administration or if the effects of the benzodiazepine persist.

LABORATORY TESTS: No specific laboratory tests are recommended to follow the patient's response or to identify possible adverse reactions.

DRUG/LABORATORY TEST INTERACTIONS: The possible interaction of flumazenil with commonly used laboratory tests has not been evaluated.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Carcinogenesis: No studies in animals to evaluate the carcinogenic potential of flumazenil have been conducted.

Mutagenesis: No evidence for mutagenicity was noted in the Ames test using five different tester strains. Assays for mutagenic potential in *S. cerevisiae* D7 and in Chinese hamster cells were considered to be negative as were blastogenesis assays *in vitro* in peripheral human lymphocytes and *in vivo* in a mouse micronucleus assay. Flumazenil caused a slight increase in unscheduled DNA synthesis in rat hepatocyte culture at concentrations which were also cytotoxic; no increase in DNA repair was observed in male mouse germ cells in an *in vivo* DNA repair assay.

Impairment of fertility: A reproduction study in male and female rats did not show any impairment of fertility at oral dosages of 125 mg/kg/day. From the available data on the area under the curve (AUC) in animals and man the dose represented 120 x the human exposure from a maximum recommended intravenous dose of 5 mg.

PREGNANCY: CATEGORY C. There are no adequate and well-controlled studies of the use of flumazenil in pregnant women. Flumazenil should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Teratogenic Effects: Flumazenil has been studied for teratogenicity in rats and rabbits following oral treatments of up to 150 mg/kg/day. The treatments during the major organogenesis were on days 6 to 15 of gestation in the rat and days 6 to 18 of gestation in the rabbit. No teratogenic effects were observed in rats or rabbits at 150 mg/kg; the dose, based on the available data on the area under the plasma concentration-time curve (AUC) represented 120 x to 600 x the human exposure from a maximum recommended intravenous dose of 5 mg in humans. In rabbits, embryocidal effects (as evidenced by increased pre-implantation and post-implantation losses) were observed at 50 mg/kg or 200 x the human exposure from a maximum recommended intravenous dose of 5 mg. The no-effect dose of 15 mg/kg in rabbits represents 60 x the human exposure.

Nonteratogenic Effects: An animal reproduction study was conducted in rats at oral dosages of 5, 25 and 125 mg/kg/day of flumazenil. Pup survival was decreased during the lactating period, pup liver weight at weaning was increased for the high-dose group (125 mg/kg/day) and incisor eruption and ear opening in the offspring were delayed; the delay in ear opening was associated with a delay in the appearance of the auditory startle response. No treatment-related adverse effects were noted for the other dose groups. Based on the available data from AUC, the effect level (125 mg/kg), represents 120 x the human exposure from 5 mg, the maximum recommended intravenous dose in humans. The no-effect level represents 24 x the human exposure from an intravenous dose of 5 mg.

LABOR AND DELIVERY: The use of MAZICON to reverse the effects of benzodiazepines used during labor and delivery is not recommended because the effects of the drug in the newborn are unknown.

NURSING MOTHERS: Caution should be exercised when deciding to administer MAZICON to a nursing woman because it is not known whether flumazenil is excreted in human milk.

PEDIATRIC USE: MAZICON is not recommended for use in children (either for the reversal of sedation, the management of overdose or the resuscitation of the newborn), as no clinical studies have been performed to determine the risks, benefits and dosages to be used.

GERIATRIC USE: The pharmacokinetics of flumazenil have been studied in the elderly and are not significantly different from younger patients. Several studies of MAZICON in patients over the age of 65 and one study in patients over the age of 80 suggest that while the doses of benzodiazepine used to induce sedation should be reduced, ordinary doses of MAZICON may be used for reversal.

ADVERSE REACTIONS: SERIOUS ADVERSE REACTIONS: Deaths have occurred in patients who received MAZICON in a variety of clinical settings. The majority of deaths occurred in patients with serious underlying disease or in patients who had ingested large amounts of non-benzodiazepine drugs, (usually cyclic antidepressants) as part of an overdose.

Serious adverse events have occurred in all clinical settings, and convulsions are the most common serious adverse event reported. MAZICON administration has been associated with the onset of convulsions in patients who are relying on benzodiazepine effects to control seizures, are physically dependent on benzodiazepines, or who have ingested large doses of other drugs. (See WARNINGS.)

Two of the 446 patients who received MAZICON in controlled clinical trials for the management of a benzodiazepine overdosage had cardiac dysrhythmias (1 ventricular tachycardia, 1 junctional tachycardia).

ADVERSE EVENTS IN CLINICAL STUDIES: The following adverse reactions were considered to be related to MAZICON administration (both alone and for the reversal of benzodiazepine effects) and were reported in studies involving 1875 individuals who received flumazenil in controlled trials. Adverse events most frequently associated with flumazenil alone were limited to dizziness, injection site pain, increased sweating, headache and abnormal or blurred vision (3% to 9%).

BODY AS A WHOLE: Fatigue (asthenia, malaise), Headache, Injection Site Pain*, Injection Site Reaction (thrombophlebitis, skin abnormality, rash)

CARDIOVASCULAR SYSTEM: Cutaneous vasodilation (sweating, flushing, hot flushes)

DIGESTIVE SYSTEM: Nausea and Vomiting (11%)

NERVOUS SYSTEM: Agitation (anxiety, nervousness, dry mouth, tremor, palpitations, insomnia, dyspnea, hyperventilation)*, Dizziness (vertigo, ataxia) (10%), Emotional lability (crying abnormal, depersonalization, euphoria, increased tears, depression, dysphoria, paranoia).

SPECIAL SENSES: Abnormal Vision (visual field defect, diplopia), Paresthesia (sensation abnormal, hypoesthesia)

All adverse reactions occurred in 1% to 3% of cases unless otherwise marked.

*indicates reaction in 3% to 9% of cases.

Observed percentage reported if greater than 9%.

The following adverse events were observed infrequently (less than 1%) in the clinical studies, but were judged as probably related to MAZICON administration and/or reversal of benzodiazepine effects:

NERVOUS SYSTEM: Confusion (difficulty concentrating, delirium), Convulsions (see WARNINGS), Somnolence (stupor).

SPECIAL SENSES: Abnormal Hearing (transient hearing impairment, hyperacusis, tinnitus).

The following adverse events occurred with frequencies less than 1% in the clinical trials. Their relationship to MAZICON administration is unknown, but they are included as alerting information for the physician.

BODY AS A WHOLE: Rigors, shivering.

CARDIOVASCULAR: Arrhythmia (atrial, nodal, ventricular extrasystoles), bradycardia, tachycardia, hypertension, chest pain.

DIGESTIVE SYSTEM: Hiccup.

NERVOUS SYSTEM: Speech disorder (dysphonia, thick tongue).

Not included in this list is operative site pain that occurred with the same frequency in patients receiving placebo as in patients receiving flumazenil for reversal of sedation following a surgical procedure.

DRUG ABUSE AND DEPENDENCE: MAZICON acts as a benzodiazepine antagonist, blocks the effects of benzodiazepines in animals and man, antagonizes benzodiazepine reinforcement in animal models, produces dysphoria in normal subjects, and has had no reported abuse in foreign marketing.

Although MAZICON has a benzodiazepine-like structure it does not act as a benzodiazepine agonist in man and is not a controlled substance.

OVERDOSAGE: Large intravenous doses of MAZICON, when administered to healthy normal volunteers in the absence of a benzodiazepine agonist, produced no serious adverse reactions, severe signs or symptoms, or clinically significant laboratory test abnormalities. In clinical studies, most adverse reactions to flumazenil were an extension of the pharmacologic effects of the drug in reversing benzodiazepine effects.

Reversal with an excessively high dose of MAZICON may produce anxiety, agitation, increased muscle tone, hyperesthesia and possibly convulsions. Convulsions have been treated with barbiturates, benzodiazepines and phenytoin, generally with prompt resolution of the seizures. (See WARNINGS.)

DOSE AND ADMINISTRATION: MAZICON is recommended for intravenous use only. It is compatible with 5% dextrose in water, lactated Ringer's and normal saline solutions. If MAZICON is drawn into a syringe or mixed with any of these solutions, it should be discarded after 24 hours. For optimum sterility, MAZICON should remain in the vial until just before use. As with all parenteral drug products, MAZICON should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

To minimize the likelihood of pain at the injection site, MAZICON should be administered through a freely running intravenous infusion into a large vein.

REVERSAL OF CONSCIOUS SEDATION OR IN GENERAL ANESTHESIA: For the reversal of the sedative effects of benzodiazepines administered for conscious sedation or general anesthesia, the recommended initial dose of MAZICON is 0.2 mg (2 mL) administered intravenously over 15 seconds. If the desired level of consciousness is not obtained after waiting an additional 45 seconds, a further dose of 0.2 mg (2 mL) can be injected and repeated at 60-second intervals where necessary (up to a maximum of 4 additional times) to a maximum total dose of 1 mg (10 mL). The dose should be individualized based on the patient's response, with most patients responding to doses of 0.6 to 1 mg. (See INDIVIDUALIZATION OF DOSAGE.)

In the event of resedation, repeated doses may be administered at 20 minute intervals as needed. For repeat treatment, no more than 1 mg (given as 0.2 mg/min) should be administered at any one time, and no more than 3 mg should be given in any one hour.

It is recommended that MAZICON be administered as the series of small injections described (not as a single bolus injection) to allow the practitioner to control the reversal of sedation to the approximate endpoint desired and to minimize the possibility of adverse effects. (See INDIVIDUALIZATION OF DOSAGE.)

MANAGEMENT OF SUSPECTED BENZODIAZEPINE OVERDOSE: For initial management of a known or suspected benzodiazepine overdose, the recommended initial dose of MAZICON is 0.2 mg (2 mL) administered intravenously over 30 seconds. If the desired level of consciousness is not obtained after waiting 30 seconds, a further dose of 0.3 mg (3 mL) can be administered over another 30 seconds. Further doses of 0.5 mg (5 mL) can be administered over 30 seconds at 1-minute intervals up to a cumulative dose of 3 mg.

Do not rush the administration of MAZICON. Patients should have a secure airway and intravenous access before administration of the drug and be awakened gradually. (See PRECAUTIONS.)

Most patients with benzodiazepine overdose will respond to a cumulative dose of 1-3 mg of MAZICON, and doses beyond 3 mg do not reliably produce additional effects. On rare occasions, patients with a partial response at 3 mg may require additional titration up to a total dose of 5 mg (administered slowly in the same manner).

If a patient has not responded 5 minutes after receiving a cumulative dose of 5 mg MAZICON, the major cause of sedation is likely not to be due to benzodiazepines, and additional MAZICON is likely to have no effect.

In the event of resedation, repeated doses may be given at 20-minute intervals if needed. For repeat treatment, no more than 1 mg (given as 0.5 mg/min) should be given at any one time and no more than 3 mg should be given in any one hour.

SAFETY AND HANDLING: MAZICON is supplied in sealed dosage forms and poses no known risk to the health care provider. Routine care should be taken to avoid aerosol generation when preparing syringes for injection, and spilled medication should be rinsed from the skin with cool water.

HOW SUPPLIED: 5 mL multiple-use vials containing 0.1 mg/mL flumazenil:
Boxes of 10 (NDC 0004-6904-14).
10 mL multiple-use vials containing 0.1 mg/mL flumazenil:
Boxes of 10 (NDC 0004-6905-14).
Store at 59° to 86° F (15° to 30° C).

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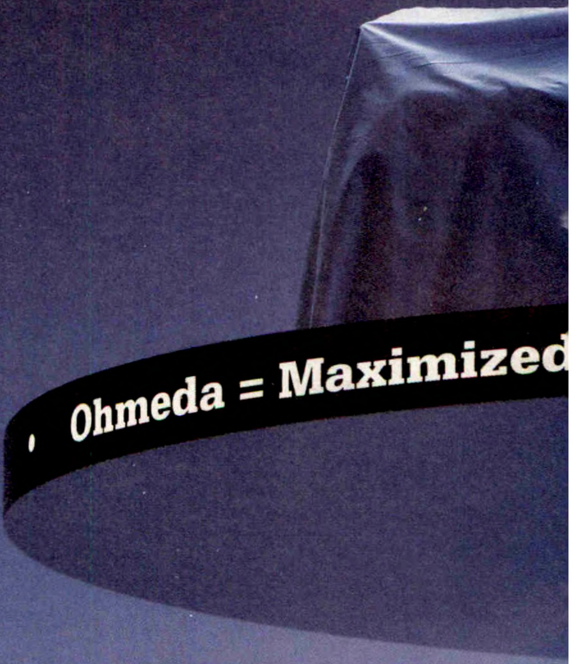

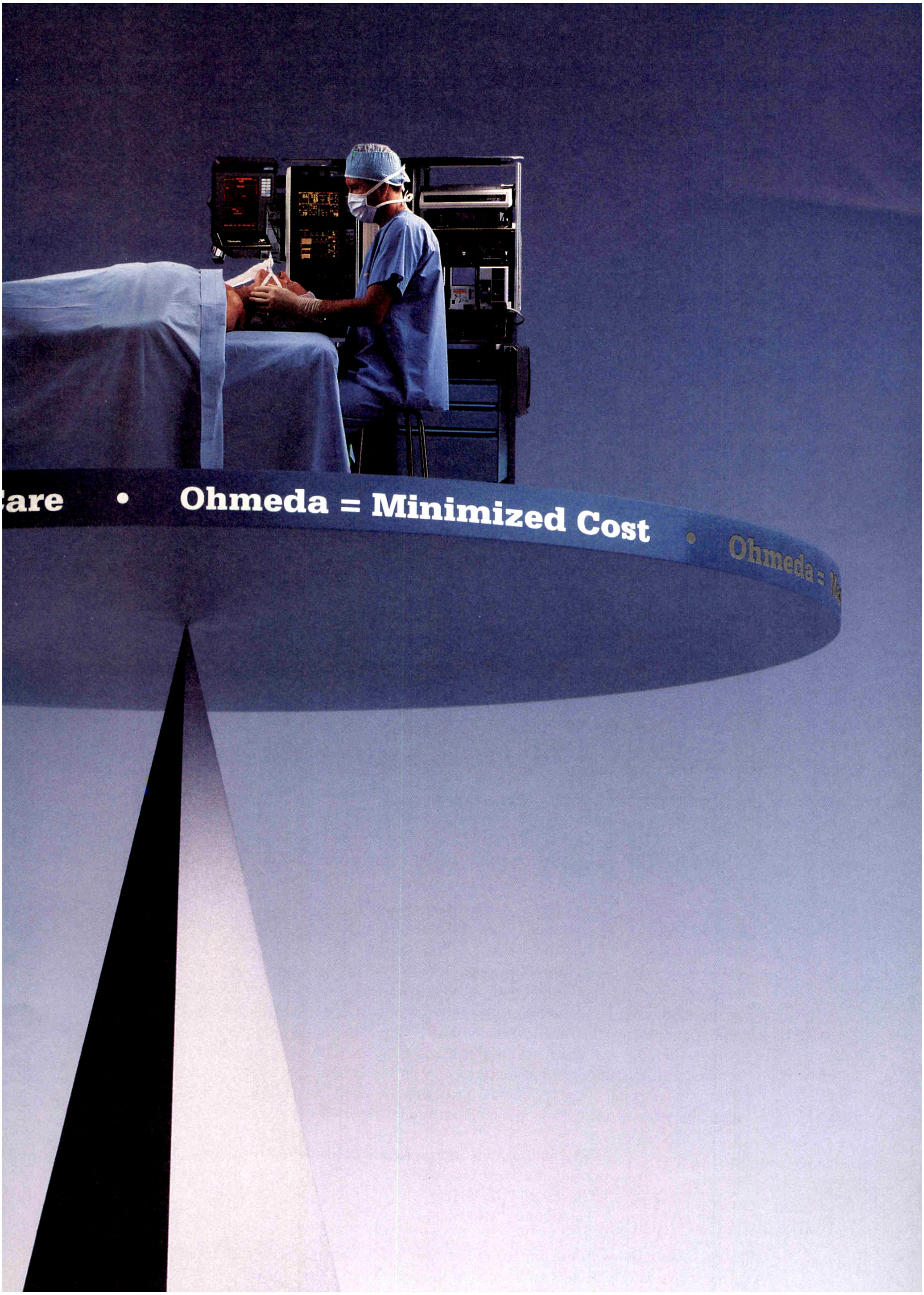
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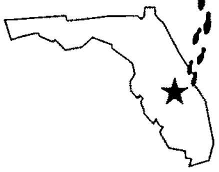

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Package Inserts and Other Dosage Guidelines Are Especially Useful With New Analgesics and New Analgesic Delivery Systems

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The introduction of new pharmaceutical compounds and new drug delivery devices and techniques usually promises increased patient benefits from improved safety, bioavailability, effectiveness, utility or convenience, and, on occasion, decreased cost. In the first few years after new drugs and devices are released, interested clinicans often informally test them for uses that were not originally intended and in patients, situations, or approaches in which they were not formally evaluated before approval. This is not only appropriate, for it may result in new uses or advantages for the products (or new safety issues), but is also expected by companies that manufacture these substances and devices and by the federal agencies that monitor and regulate their sales. We believe that it is in this spirit that the case report of Steinberg et al. (1), published in this issue, is best viewed.

Before FDA approval, the fentanyl transdermal system (Duragesic patches) used in this patient was evaluated in 357 patients in postoperative and pharmacokinetic studies (usually a single 25-, 50-, 75-, or 100-μg/h patch for 1 day for postoperative pain) and in 153 patients with chronic cancer pain (one to multiple patches, 25–600 μg/h of fentanyl for 1–866 days) (2–4). Most of the patients receiving Duragesic for postoperative pain were opioid naive (not tolerant to opioids), and most of those receiving the patches for chronic pain were considered tolerant to opioids owing to chronic opioid therapy (2–4).

Duragesic caused hypoventilation, defined as a respiratory rate <8 breaths/min or a $Paco_2$ >55 mm Hg, in 13 (3.6%) of the opioid-naive patients. None of the patients with 25- or 50-μg/h patches experienced hypoventilation (2–4). However, 6 of the 177 patients (3.4%) given 75-μg/h and 7 of the 105 patients (6.6%) given 100-μg/h patches for postoperative pain experienced hypoventilation. Nine of the 13 patients (69%) experiencing hypoventilation and receiving Duragesic for postoperative pain were <63 kg, and 10 were women (2–4). Twenty-five patients received Duragesic (100 μg/h) after thoracic surgery, and four of these experienced respiratory depression (16%) (2–4). In contrast, 3 of 80 (4%) of the patients receiving the same dose of Duragesic after nonthoracic surgery sustained respiratory depression. Only 3 of the 153 opioid-tolerant patients (2%) receiving Duragesic for chronic cancer pain experienced hypoventilation (2–4).

Significant respiratory depression, defined as a 50% reduction in the ventilatory response to CO_2, has generally been found to begin with fentanyl plasma concentrations in the range of 2–3 ng/mL (5–6). In the pre-FDA approval studies, no patients exposed to Duragesic (25 μg/h) experienced a maximum plasma fentanyl concentration of 2 ng/mL or above, and only 3% of patients exposed to 50-μg/h patches had a plasma concentration of fentanyl >2 ng/mL (all between 2 and 3 ng/mL) (2). In contrast, 15% and 31% of patients exposed to the 75- and 100-μg/h patches, respectively, had maximum plasma fentanyl concentrations of 2–3 ng/mL, and 4% and 11%, respectively, had plasma fentanyl concentrations >3 ng/mL (2).

Of the 357 non-opioid-tolerant patients receiving Duragesic, 5 (1.4%) (1 after 75 μg/h and 4 after 100 μg/h) were reported to be confused after Duragesic, whereas 1 patient (<1%) was agitated, 1 experienced depersonalization, 1 hallucinations, and 1 hostility (3). Of the 153 patients receiving Duragesic for chronic cancer pain, 20 (13%) were reported to be confused, 5 (3%) reported hallucinations, 5 reported anxiety, 2 (1%) reported agitation, and 2 experienced a paranoid reaction (3).

We believe that the above data are important because as a result, the pharmaceutical companies that developed Duragestic (Janssen Pharmaceutica and Alza Corp.) and the FDA agreed that Duragesic should only be indicated in the management of

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chronic pain in opioid-tolerant patients requiring opioid analgesia (4). They did not recommend Duragesic in the management of postoperative pain because it was believed that the product had not been adequately studied and resulted in an unacceptable incidence of hypoventilation in these patients (4). They concluded that it was not possible from the available data to identify factors that could be used to select a dose of Duragesic that would be safe and effective in individual postoperative patients.

The Duragesic package insert warns that Duragesic doses >25 μg/h are too large for initiation of therapy in non-opioid-tolerant patients and should not be used to begin Duragesic therapy in those patients (4). It further warns that there has been no systematic evaluation of Duragesic as an initial opioid analgesic in the management of chronic pain, because most patients in the clinical trials were converted to Duragesic from other narcotics. It suggests that patients be converted to Duragesic by:

1. Calculating the previous 24-h analgesic requirement
2. Converting this amount from an equianalgesic oral morphine dose using a conversion table supplied in the insert
3. Choosing a Duragesic dose based on an oral or intramuscular morphine equivalence dose schedule also published in the package insert
4. Initiating Duragesic treatment using the recommended dose and titrating patients upward (*no more frequently than every 3 days after the initial dose or every 6 days thereafter*) until analgesic efficacy is attained because it may take up to 6 days after increasing the dose of Duragesic for the patient to reach equilibrium on the new dose. *During the initial application of Duragesic, it is advised that patients should use short-acting analgesics* for the first 24 h, as needed, until analgesic efficacy with Duragesic is attained. Thereafter, some patients still may require periodic supplemental doses of other short-acting analgesics for "breakthrough" pain. Appropriate dosage increments should be based on the daily dose of supplementary opioids using the ratio of 90 mg/24 h of oral morphine to a 25-μg/h increase in Duragesic dose.

Finally, the package insert advises that initial doses of Duragesic should be reduced in elderly, cachectic, or debilitated patients because of poor fat stores, muscle wasting, or altered clearance (4). The insert also suggests reducing the Duragesic dose in patients receiving other central nervous system depressants (a dose reduction of 50% or more is suggested) because of potentiation of action.

The patient presented by Steinberg et al. (1) was cachectic, elderly (71 yr old), and azotemic. It is unclear whether she was opioid tolerant when treatment started, but she clearly was experiencing opioid effects on admission to the hospital and up until the 10th day of admission. These effects included confusion, agitation, hallucination, disorientation, restlessness, paranoia, and pinpoint pupils. These types of opioid effects have been described after the use of all μ-receptor agonists and most δ-, κ-, and σ-agonists as well (2–4,7). Therefore, it is not necessary to postulate the accumulation of the metabolite norfentanyl as the mechanism for the reported side effects. Although normeperidine toxicity (due to central nervous system stimulation) after meperidine is highly correlated to increases in plasma concentration of the metabolite (8), whether norfentanyl can also cause these problems is unknown, and as far as Janssen Pharmaceutica knows (per a telephone conversation with J. Heykants, PhD), it has never been tested in humans or any other animal. Norfentanyl is less potent than either fentanyl or meperidine in the isolated guinea pig ileum contraction test, a test of opioid agonist activity (9). Norfentanyl is also rapidly metabolized to despropionyl norfentanyl (10). This pathway is only disrupted in patients with hepatic failure. Thus, there is little reason that norfentanyl should have accumulated, even though the patient's renal function was abnormal.

An additional possible cause of the patient's confusion, as indicated by the authors, was hypoxemia. A metanalysis was accomplished by FDA reviewers during the Duragesic New Drug Application review using plasma fentanyl concentrations obtained from both opioid-tolerant and non-opioid-tolerant patients (11). This analysis predicted that if Duragesic (50 μg/h) was used in opioid-naive patients weighing 50–74 kg and Duragesic (75 μg/h) in patients weighing 75 kg or more, then 3% of the patients would be expected to have a plasma fentanyl concentration between 2 and 2.5 ng/mL and a 15% risk of hypoventilation. The analyses also indicated that 1.5% of the patients would experience a fentanyl plasma concentration of 2.5–3.0 ng/mL and a 25% risk of hypoventilation. As mentioned earlier, it is unclear whether the patient in question was opioid naive, at least at the beginning of her exposures to Duragesic. However, within 4 days of initiating Duragesic therapy, the patient's dose of fentanyl had been increased from 25 to 125 μg/h. The Duragesic package insert specifically warns against this type of rapid increase in dosage because, although peak plasma concentrations of fentanyl after a single-patch application usually occur by 18–24 h, new peaks can occur even later (4). Thus, the risk of producing higher than expected plasma concentrations of fentanyl and hypoventilation are increased with this approach. The package insert also suggests that short-acting analgesic supplements be used as needed during the slow upward titration of Duragesic dosage, rather than the sustained-release morphine used in this case. Finally, as mentioned earlier, the package insert indicates that, at least at the time of Duragesic approval, all studies with Duragesic in patients with chronic cancer pain had been accomplished in opioid-tolerant patients taking other narcotics who were then converted to Duragesic. It warns that no systematic evaluation of Duragesic as an initial opioid analgesic in this patient population had yet been accomplished.

By the fifth day after admission (the ninth day after beginning Duragesic), the patient reported by Steinberg et al. (1) was receiving 2 mg of lorazepam and two 60-mg sustained-release morphine tablets during the day plus 125 μg/h of Duragesic. The additional compounds were administered despite the package insert warnings suggesting that central nervous system depressants should be decreased, not increased, with initial Duragesic application because of the increased risk of hypoventilation and hypotension.

Physicians in America and most of western civilization are not bound to administer drugs or practice medicine according to package insert-suggested guidelines. Our freedom, in this regard, allows new discoveries (good and bad) to be made every day. However, we believe that it is prudent to consider package insert and other medical publication guidelines carefully, especially soon after a new drug or drug delivery device becomes available. We also believe that although it is unclear what caused this patient's adverse effects, greater awareness of the different dynamics of transdermal fentanyl delivery (versus more traditional fentanyl administration techniques) is one benefit that may result from her experience.

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Propofol Requirements for Induction of Anesthesia in Children of Different Age Groups

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To demonstrate any age-related differences in propofol requirements for induction of anesthesia, 150 healthy children aged 3–5 yr ($n = 50$), 6–9 yr ($n = 50$), and 10–15 yr ($n = 50$) scheduled for outpatient surgery were randomly assigned to receive an induction dose of propofol of 1.5, 2.0, 2.5, 3.0, or 3.5 mg/kg. To limit pain during injection, alfentanil (5 μg/kg) was administered before the propofol. Patients were classified as asleep or not asleep 30 s after the propofol. Incidence of excitation, injection pain, and apnea during induction of anesthesia were noted; arterial blood pressure and heart rate were recorded for 5 min after induction. More than 95% of the children were asleep in the dose groups receiving ≥2.5 mg/kg. The number of patients falling asleep after receiving 1.5 mg/kg of propofol increased significantly with increasing age ($P < 0.05$); the difference between the oldest and the youngest age groups was the most significant ($P < 0.05$). Significant decreases in mean arterial blood pressure and heart rate occurred after induction in all dose and age groups without any systematic intergroup differences. Apnea occurred more frequently in older children ($P < 0.01$) and with larger doses ($P < 0.01$). The most frequent side effect was erythema near the site of injection, and its occurrence was dose dependent. The authors conclude that 2.5 mg/kg of propofol, if preceded by 5 μg/kg of alfentanil, is an appropriate induction dose for children aged 3–15 yr and that the sleep response to 1.5 mg/kg is more in older children.

(Anesth Analg 1992;75:876–9)

Propofol is a useful anesthetic for outpatient surgery because it offers rapid recovery and has few side effects. In children, however, uncertainty has existed concerning dose requirements. Morton et al. (1) found that doses generally used for adults are also effective in children. Others report that children need more propofol than adults (2–5), which concurs with the study of Jonmarker et al. (6) in relation to thiopental requirements for anesthesia. Comparison among different studies is difficult owing to the different premedication regimes used. In comparing thiopental with propofol, Meursing et al. (7) suggested that a dose >2.5 mg/kg of propofol might be required to suppress excitatory phenomena in younger children. The authors attempted to determine propofol requirements for induction of anesthesia in children of different age groups.

Methods

Approval of the Human Research Committee and informed parental consent were obtained. One hundred fifty children, ASA physical status I or II, scheduled for elective outpatient surgery were assigned to three age groups (50 children per group): 3–5, 6–9, and 10–15 yr. They were further randomly assigned to five dose groups: 1.5, 2.0, 2.5, 3.0, and 3.5 mg/kg of propofol by blind drawing of tickets.

Most children were accompanied by one parent during induction of anesthesia. Before induction, baseline measurements of arterial blood pressure, heart rate, and O_2 saturation (Biox 3700 pulse oximeter, Ohmeda, Louisville, Colo.) were made. Venous access was established in the dorsum of the hand with a 22- or 20-gauge cannula. Thus far, the children received no premedication.

To limit pain during injection of propofol, 5 μg/kg of intravenous alfentanil was administered, and 20–30 s later the allocated dose of propofol was

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injected over 10–15 s. During induction of anesthesia, the patients were observed for pain during injection and for excitation by an anesthesiologist unaware of the experimental treatment. Withdrawal of the hand, verbal expression of pain, grimacing, and starting to cry were interpreted as pain during injection; other spontaneous movements were called excitation. Any local reactions and other side effects were also noted, particularly apnea requiring controlled ventilation. If apnea occurred after administration of propofol that lasted longer than 1 min or caused the O_2 saturation to decrease below 90%, ventilation was controlled until spontaneous ventilation was resumed. Thirty seconds after injection of propofol, an assessment was made as to whether the patient was asleep. The same assessor, who was unaware of the study treatment, classified the patient as asleep if the eyelash reflex was negative and there was no response (gross movement) to application of the face mask. If either of these criteria were not fulfilled, the patient was classified as not asleep; in that case, an additional dose of 1 mg/kg of propofol was administered and repeated as required until the patient was deemed asleep.

Once asleep, patients were allowed to spontaneously breathe 70% N_2O and 30% O_2. Arterial blood pressure, heart rate, and O_2 saturation measurements were made at 30, 60, 120, 180, and 300 s after the first propofol injection. At the same intervals, patients were again classified as asleep or not asleep. Any patients who, according to the criteria mentioned earlier, awoke during the 5-min observation period, were given an additional dose of 1 mg/kg of propofol.

After the 5-min observation period, anesthesia was continued as considered appropriate. Three to four hours postoperatively, the patients were assessed as either fully awake or drowsy. We also noted whether any nausea was felt (according to the patient or the parent's impression) and whether the child had vomited at least once; appetite was evaluated as good if the patient had already started eating solids without any problem or if he or she wanted to eat something. These postoperative assessments were not necessarily made by a blinded assessor. In addition, local skin reactions to the propofol and other side effects were recorded.

In statistical analysis of arterial blood pressure and heart rate observations, we included only those patients who did not need an additional dose of propofol to fall asleep so as to keep the groups comparable. Of the apneas requiring controlled ventilation, those occurring after an additional dose of propofol were not counted.

The principal categorical variables are presented in the form of contingency tables according to dose and age groups. Statistical analysis of differences between groups was carried out using χ^2-tests and two-sided Fisher's exact probability test as appropriate (8).

Table 1. Demographic Data of 150 Children Undergoing Elective Outpatient Surgery

	M/F	Age (yr)	Weight (kg)
Dose group (mg/kg)			
1.5	20/10	8.6 ± 3.4	31.8 ± 13.5
2.0	19/11	7.9 ± 2.8	28.9 ± 11.1
2.5	23/7	8.3 ± 3.2	30.8 ± 13.0
3.0	24/6	8.2 ± 3.6	31.0 ± 13.3
3.5	21/9	7.8 ± 3.4	29.5 ± 13.4
Age group (yr)			
3–5	35/15		
6–9	37/13		
10–15	35/15		
Total	107/43		

M, male; F, female.
Values for age and weight are mean ± SD.

Continuous variables are presented as mean ± SD. Mean percentage decreases of mean arterial blood pressure and heart rate between baseline and 300 s after injection of propofol were calculated according to age and dose groups. To these two variables a two-factor (age and dose) analysis of variance (GLM-procedure in Statistical Analysis System [SAS]) was applied (9), with linear contrasts in dose groups. A P value <0.05 was considered statistically significant.

Results

Owing to the predominance of male genital surgery, 107 boys and 43 girls participated in the study. Age, weight, and gender distribution were similar in the five dose groups (Table 1). Pain on injection of propofol was observed in 6 of 150 patients (4%). Excitation was noted in 25 of 150 patients (17%). There was no significant difference in the incidence of pain or excitation among age or dose groups.

The number of patients asleep 30 s after administration of each propofol dose is shown in Table 2. The dose groups receiving ≥ 2.5 mg/kg had $>95\%$ sleep response to the respective dose. When considering the age groups separately (Table 2), the 1.5-mg/kg dose group showed statistically significant differences ($P < 0.05$) among the age groups: the older the patients, the more fell asleep at this dose. The difference between the oldest and the youngest age groups was the most significant ($P < 0.05$). Within the other dose groups, differences among age groups were not statistically significant.

Apnea requiring controlled ventilation occurred in 21.6% of the patients. The percentages for the differ-

Table 2. Number of Patients Asleep 30 s After Propofol Administration

Age group (yr)	Dose (mg/kg)				
	1.5^a	2.0	2.5	3.0	3.5
3–5	3	10	10	10	10
6–9	6	9	10	10	10
10–15	9^b	8	9	10	10
Total	18 (60%)	27 (90%)	29 (97%)	30 (100%)	30 (100%)

[a] $P < 0.05$ overall.
[b] $P < 0.05$ vs youngest age group.

Table 3. Circulatory and Ventilatory Observations by Age and Dose Group

	Patients requiring controlled ventilation (%) (n = 148)	Decrease of MAP (%) (n = 129)	Decrease of HR (%) (n = 129)
Age group (yr)			
3–5	12.2	20.8 ± 12.6	12.3 ± 14.8
6–9	14.3 ^{a}	24.0 ± 6.9	17.4 ± 11.0
10–15	38.0	24.8 ± 8.1	15.9 ± 12.0
Dose group (mg/kg)			
1.5	6.9	20.6 ± 7.7	11.2 ± 8.0
2.0	3.4	23.2 ± 7.2	20.3 ± 9.0
2.5	28.1 ^{a}	21.2 ± 12.8	13.6 ± 10.3
3.0	31.0	25.7 ± 9.2	14.3 ± 17.2
3.5	37.9	24.8 ± 8.5	16.1 ± 13.6
Total	21.6	23.3 ± 9.5	15.3 ± 12.7

MAP, mean arterial blood pressure; HR, heart rate.
Values for decrease of MAP and decrease of HR are mean ± SD.
[a] $P < 0.01$.

ent age and dose groups are shown in Table 3. There was a significant relation to age and dose, in that controlled ventilation was required more often in older children ($P < 0.01$) and at larger doses ($P < 0.01$).

The mean percentage decreases in mean arterial blood pressure and heart rate from baseline to 300 s are shown in Table 3 for the five dose groups and the three age groups. There was no significant overall difference among dose or age groups. When using linear contrasts, some dose-group percentages showed differences ($P < 0.05$): 1.5 versus 2.0 mg/kg, 2.0 versus 2.5 mg/kg (heart rate decrease), and 1.5 versus 3.0 mg/kg (arterial blood pressure decrease).

Postoperative alertness assessment showed that 139 of 147 patients (95%) were fully awake and 8 of 147 (5%) were drowsy. In three patients, this assessment was erroneously omitted. Nausea occurred in 26% and vomiting in 19% of the patients. Incidence of vomiting was significantly less frequent ($P < 0.05$) in the 3–5-yr age group (6%) than in the 6–9- and 10–15-yr age groups (23% and 29%, respectively). Postoperatively, 53% of the patients had good appetite.

Erythema near the site of injection occurred in seven patients in the 3.0- and 3.5-mg/kg dose groups only; this dose dependency was significant ($P < 0.05$). Other minor side effects were skin rash on the chest (four patients) and hiccup, minor bronchospasm, and myoclonia (each in one patient). These side effects showed no significant relation to age or dose. None of the side effects needed intervention.

Discussion

The results indicate that a dose of 2.5 mg/kg of propofol is sufficient to induce sleep (according to the criteria set forth in Methods) in children aged 3–15 yr. Preadministration of alfentanil may account for this dose requirement being lower than that reported by Patel et al. (5) and Westrin (10). Hannallah et al. (11) reported the same dose requirements in children aged 3–12 yr as in this study but without pretreatment with alfentanil; they used the large antecubital vein and thus avoided pain on injection. Aun et al. (12) also found dose requirements for propofol induction comparable to ours.

Maturational changes during infancy and childhood may result in age-related differences in pharmacodynamic and pharmacokinetic properties of drugs. Thus, we postulate that maturational changes may produce different responses to propofol among children of different age groups. The results of this dose-response study, at least those of the 1.5-mg/kg dose group, indicate that the response is enhanced with increasing age. This is in accordance with the findings of Jonmarker et al. (6) who found a markedly greater dose requirement for thiopental induction in infants than in older children. Westrin (10) reported a less marked but still significant difference in dose requirements between the same two age groups as in the Jonmarker et al. (6) study, when propofol was used instead of thiopental. Recently, Aun et al. (12) demonstrated that young children need more propofol than older children. Possible explanations for this phenomenon may be age-related differences in cardiac output in relation to body weight, resulting in differences in the arterial peak concentration reaching the brain, and age-related differences in pharmacodynamics. However, Hannallah et al. (11) did not find any age-related differences in dose requirements. Arterial blood pressure and heart rate decreased in all patient groups but without clinical consequences. This is in accordance with some other studies in children (2,7,8,13). Other authors, however, report a stable heart rate (1,4,11). Although hemodynamic differences were demonstrable between some dose groups, there was no systematic relation with the dose. Our results correspond well with the findings of Short and Aun (13) who reported somewhat greater decreases of arterial blood pressure and heart rate, but their patients breathed halothane during the 5-min observation period; they, too, were unable to demonstrate any dose-related differences in hemodynamic changes.

Pain during injection is an established problem with propofol (7). Because alfentanil is effective in limiting this pain (14), we considered its omission unethical. The 4% incidence of pain with alfentanil recorded in this study compared with 20% without it in a previous study (7) confirms the efficacy of alfentanil.

The incidence of excitation is not age or dose related, which refutes our suggestion (7) that relatively high doses may be required to suppress excitation, especially in younger children. Apnea requiring controlled ventilation occurred in 21.6% of the patients, which is very similar to the results of Hannallah et al. (11) and Westrin (10), who found an incidence of apnea of 21% and 18%, respectively. Ventilatory changes were clearly related to both dose and age. The fact that older children had more apnea and showed a better sleep response to the 1.5-mg/kg dose suggests that other immediate effects of propofol could also be age dependent, but we failed to demonstrate this with respect to hemodynamic changes. Hannallah et al. (11) did not find any age-related differences at all, and the correlation that they found between dose and apnea incidence was not significant.

The data on postoperative assessment of alertness, nausea, and vomiting are difficult to evaluate realistically owing to a lack of standardized anesthetic technique and the varying duration of procedures (10 min–2 h). Nevertheless, 95% of the patients were fully awake 3 h postoperatively; this does not conflict with the general opinion that recovery from propofol is rapid.

All side effects observed in this study were minor. The most frequently occurring side effect was local redness, which occurred only with those doses higher than that needed to anesthetize most patients.

The authors conclude that in healthy children aged 3–15 yr, a dose of 2.5 mg/kg of propofol induces sleep in >95% of patients if preceded by alfentanil (5 μg/kg), which is effective in limiting pain on injection. A remarkable and statistically significant age-related difference was found both in sleep-inducing effects of 1.5 mg/kg of propofol and in the incidence of apnea, to the effect that younger children are more resistant. The most frequent side effect was local redness, which occurred only with doses >2.5 mg/kg. On the basis of these results, a clear age-related dose recommendation cannot be made, but 2.5 mg/kg would seem a reasonable guideline for the induction dose of propofol in children aged 3–15 yr.

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Effectiveness of Preoperative Sedation With Rectal Midazolam, Ketamine, or Their Combination in Young Children

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To determine which of three types of rectal sedation was most effective preoperatively in facilitating parental separation and intravenous cannulation in young children, 100 children 3.0 ± 1.7 (mean ± SD) yr of age were randomly assigned to four equal groups. One group (M-K-A) received rectal midazolam (0.5 mg/kg), ketamine (3 mg/kg), and atropine (0.02 mg/kg). The other sedation groups received the same doses of midazolam and atropine (M-A) or ketamine and atropine (K-A) alone, and the control group (A) received only rectal atropine. Most children in either the M-K-A (100%) or M-A (92%) groups separated easily from their parents without struggling or crying, significantly more than in the K-A (60%) or A (64%) groups. However, more children in the M-K-A group (44%) were asleep during separation than in the M-A group (8%; $P < 0.05$). Only 20% of the children in the M-A or M-K-A groups cried during intravenous catheter placement, significantly less than in the K-A (56%) or A (92%) groups. Intravenous catheter placement was also successful significantly more often in the M-A (80%) and M-K-A (84%) groups than in the K-A (48%) or A (40%) groups. Complications were similar among the groups, but there was evidence that midazolam prolonged recovery time in some patients. Rectal midazolam with or without ketamine is a useful technique when intravenous catheter placement before induction of anesthesia is desired.

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The presence of an intravenous (IV) catheter before induction of anesthesia in a young child gives the anesthesiologist the option of performing an IV induction of general anesthesia and provides a means of rapidly administering medications should complications during the induction occur. However, pain, anxiety, and fear of needles and of parental separation can make IV cannulation before induction of anesthesia difficult in infants and young children. In addition, painful, frightening venopunctures may cause long-term psychological complications in children and make subsequent contacts with health professionals more difficult, particularly in patients who require multiple anesthetics and procedures (1).

The use of midazolam administered rectally to facilitate IV catheterization in young children before induction of anesthesia was previously investigated by DeJong and Verburg (2). They found that the response of children to IV placement who were given midazolam (0.5 mg/kg) rectally before IV catheterization was similar to a group of children given midazolam (0.15 mg/kg) intramuscularly, but without the crying and pain associated with an intramuscular injection. They did not, however, have a control group with which to compare the effectiveness of either rectal or intramuscular midazolam, their observers were not blinded to the drugs administered, and their patients were not completely randomized.

We hypothesized that a combination of midazolam, ketamine, and atropine administered rectally would significantly diminish the pain, fright, and struggling often associated with IV catheter placement in young children and increase the probability of successful IV placement. Midazolam would provide sedation and might diminish recall of the IV catheter placement or other procedures associated with surgery or anesthesia (2–5). Ketamine would diminish the pain associated with IV cannulation as well as provide sedation (6). Atropine would counteract the hypersalivation often seen with the use of

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ketamine and has been found effective when combined with either ketamine (6) or midazolam (2) administered rectally.

In a preliminary, uncontrolled investigation, we found that a combination of midazolam (0.5 mg/kg), ketamine (3 mg/kg), and atropine (0.02 mg/kg) appeared to attenuate the response to IV cannulation without causing excessive sedation. The purpose of this randomized, single-blind study was to determine whether this combination of midazolam, ketamine, and atropine was superior to a combination of the same dose of midazolam and atropine alone, ketamine and atropine alone, or to a control group receiving only rectal atropine in providing sedation for separation and for preinduction IV cannulation in young children.

Methods

After University of Minnesota Human Subjects Committee approval and parental consent, 100 ASA physical status I, II, and III patients ranging in age from 8 mo to 7 yr scheduled to undergo a variety of elective surgical procedures were randomly assigned to four groups of 25 patients each. The control group (group A) received atropine (0.02 mg/kg). Group K-A received ketamine (3 mg/kg) and atropine (0.02 mg/kg). Group M-A received midazolam (0.5 mg/kg) and atropine (0.02 mg/kg). Group M-K-A received midazolam (0.5 mg/kg), ketamine (3 mg/kg), and atropine (0.02 mg/kg). All drugs were administered rectally with a 2.0-mm pediatric feeding tube (Pharmaseal) lubricated with sterile lubricant (Surgilube) and inserted 7–10 cm beyond the anal opening.

A child psychologist unaware of the drug(s) administered, observed the children preoperatively, at induction of anesthesia, on emergence, and postoperatively in the recovery room. The level of sedation was graded for each child (a) before administration of rectal medication; (b) during insertion of the rectal catheter; (c) immediately after administration, (d) 10 min after administration; and (e) at separation from the parents (15 min after administration). Patients were graded at each time interval as follows: 1 = asleep; 2 = calm but awake; 3 = restless; 4 = crying and upset. The pulse and respiratory rates were recorded before the administration of the sedative and 10 min after administration. Arterial oxygen saturation was recorded on arrival in the operating room before the administration of oxygen and then throughout the perioperative period.

In the operating room, an IV catheter was placed or attempted by the staff anesthesiologist responsible for the case. Ninety-seven patients had 1% lidocaine injected subcutaneously with a 28-gauge needle before placement of the IV catheter. Three patients, one each from the A, M-A, and M-K-A groups, had catheters placed or attempted without the local anesthetic. The response to the IV catheter placement was graded by the child psychologist at three times: (a) when the patient's hand or foot was held, and he was approached with a needle; (b) when the skin was infiltrated with lidocaine; and (c) when the IV catheter was placed. Children were graded at each point as 1 = asleep/obtunded—no response to approach with needle, lidocaine instillation, or IV placement; 2 = calm—awake but no crying or withdrawal when approached by needle, local infiltration, or catheter placement; 3 = withdraws but allows—pulls away with stimulus but no crying; or 4 = crying—uncooperative and struggling with stimulation. The success or failure of the IV catheter placement was also noted, and the number of attempts before the catheter was successfully placed was recorded. No child received more than two unsuccessful IV attempts before a mask induction of anesthesia was performed. The anesthesiologist's opinion as to the ease of the IV placement (satisfactory or unsatisfactory) was also recorded.

After successful IV placement, general anesthesia was induced with IV thiopental followed by a skeletal muscle relaxant. If the IV placement was unsuccessful, anesthesia was induced with nitrous oxide and halothane via face mask. The response to the application of a face mask if the IV catheter was unable to be placed was graded by the child psychologist as either 1 = calm—no restraint necessary, or 2 = restless/struggling—restraint required.

The complications of either IV or mask induction of anesthesia, including (a) laryngospasm, (b) arterial oxygen saturation <90%, (c) emesis, and (d) excessive salivation, were noted by the attending anesthesiologist and recorded by the child psychologist. Postoperative complications, including (a) laryngospasm, (b) arterial oxygen saturation <90%, (c) excessive salivation, (d) nausea and vomiting, and (e) postextubation croup, were also noted by the attending anesthesiologist and recorded by the child psychologist, as was the time to extubation. Intraoperative and postoperative narcotic usage was also recorded for each patient.

In the postanesthesia recovery room (PACU), the patients were assigned a numerical score using a modified Aldrete (7) scale by the PACU nurse every 30 min. The scale assigns a score between 0 and 2, 2 being normal in each of five categories: respiration, activity, alertness, blood pressure, and temperature. The children were discharged if the modified Aldrete score was >8, with a minimal score of 2 in the respiration, activity, and alertness categories, and after being examined by the attending anesthesiologist. The time from the end of surgery until the patients were discharged from the PACU was recorded and compared among the groups. A pro-

Table 1. Demographic Characteristics of the 100 Children Receiving Preoperative Rectal Sedation or the Control Solution

	Rectal solutions			
	M-K-A	M-A	K-A	A
Age (yr)	2.7 ± 1.4	3.3 ± 1.8	3.5 ± 1.9	2.6 ± 1.8
Age range (yr)	0.7–6.0	0.8–7.0	0.7–6.0	0.7–7.0
Weight (kg)	14.5 ± 5.7	16.0 ± 5.5	16.4 ± 5.0	13.9 ± 3.7
Gender (M/F)	16/9	17/8	16/9	17/8
ASA physical status (I/II, III)	22/3	20/5	23/2	22/3
Type of surgery				
General and urologic	12	9	9	13
Eye, ear, nose, and throat	9	13	12	8
Other	4	3	4	4
Duration of surgery (h)	2.2 ± 1.1	2.1 ± 1.2	2.3 ± 1.4	2.6 ± 1.6

M-K-A, midazolam (0.5 mg/kg), ketamine (3 mg/kg), and atropine (0.02 mg/kg); M-A, midazolam (0.5 mg/kg) and atropine (0.02 mg/kg); K-A, ketamine (3 mg/kg) and atropine (0.02 mg/kg); A, atropine (0.02 mg/kg) (control).

Data presented are mean values ± SD (or No. of patients).

longed discharge time was defined as a discharge time of >30 min.

Results were reported as mean ± SD or percentage. Comparisons among groups were made using the χ^2 method with Yates' correction for continuity for categorical data and analysis of variance for continuous variables. Significance was defined as $P < 0.05$.

Results

The mean age (± SD) of the patients was 3.0 ± 1.7 yr, and the mean weight was 15.2 ± 5.1 kg. There were no significant differences among the four groups in age, weight, gender, ASA physical status, and length or type of operation (Table 1).

Rectal administration of drugs caused transient distress in some patients, but by 10 min most patients were calm. Although most patients who received midazolam and atropine alone separated calmly from their parents, significantly more patients who received all three drugs were asleep at separation than those who received midazolam and atropine alone, ketamine and atropine alone, or the control solution (Figure 1).

The response to IV catheterization and success rate of IV catheterization were improved in both groups that received midazolam. However, similiar to the response to parental separation, significantly more children who received all three drugs were asleep when approached by the anesthesiologist and a needle (Figure 2). Eighty-four percent of intravenous catheters in the M-A group and 80% in the M-K-A group were successfully placed, both significantly greater ($P < 0.05$) than the success rate for the patients who received ketamine and atropine (48%) or rectal atropine alone (40%). The anesthesiologists also thought that the child's response to cannulation was satisfactory more often in the M-A (84%) and M-K-A (76%) groups than the K-A (48%) and A (28%) groups (M-A vs K-A or A, $P < 0.05$; M-K-A vs K-A or A, $P < 0.05$).

Of the four patients in the M-A and five patients in the M-K-A groups in which IV catheterization failed, two in the M-K-A (40%) and two in the M-A (50%) groups, respectively, required restraint for the application of a face mask for the inhalation induction of anesthesia. In contrast, 9 of the 11 patients in the K-A group (82%) and 14 of the 15 (93%) patients in the A group in whom IV cannulation failed required restraint for the mask induction of anesthesia, significantly greater than the groups receiving midazolam (M-A plus M-K-A vs K-A plus A; $P < 0.05$).

There was no difference in the percentage of patients who had laryngospasm (A, 4%; K-A, 4%; M-A, 0%; M-K-A, 4%), excessive salivation (A, 4%; M-A, 0%; K-A, 0%; M-K-A, 0%), emesis (A, 4%; M-A, 0%; K-A, 0%; M-K-A, 0%), or oxygen saturation to <90% (A, 4%; K-A, 0%; M-A, 0%; M-K-A, 0%) on induction of anesthesia among the four groups. There was no change in the heart or respiratory rates during the preoperative study period in any of the four groups. The mean room air arterial oxygen saturation before induction of anesthesia but after administration of the rectal solutions was similar in the A (99% ± 1%), K-A (98% ± 2%), M-A (100% ± 1%), and M-K-A (99% ± 2%) groups.

The percentage of patients who received narcotics intraoperatively was similar in the M-K-A (75%), M-A (56%), K-A (76%), and A (60%) groups, as was the percentage of patients requiring narcotics in the recovery room: M-K-A (24%), M-A (32%), K-A (40%), and A (32%).

There also was no difference in the percentage of patients among each group who on emergence from anesthesia had laryngospasm (A, 12%; K-A, 4%; M-A, 4%; M-K-A, 8%), oxygen saturation <90% (A, 8%; K-A, 8%; M-A, 0%; M-K-A, 8%), excessive sali-

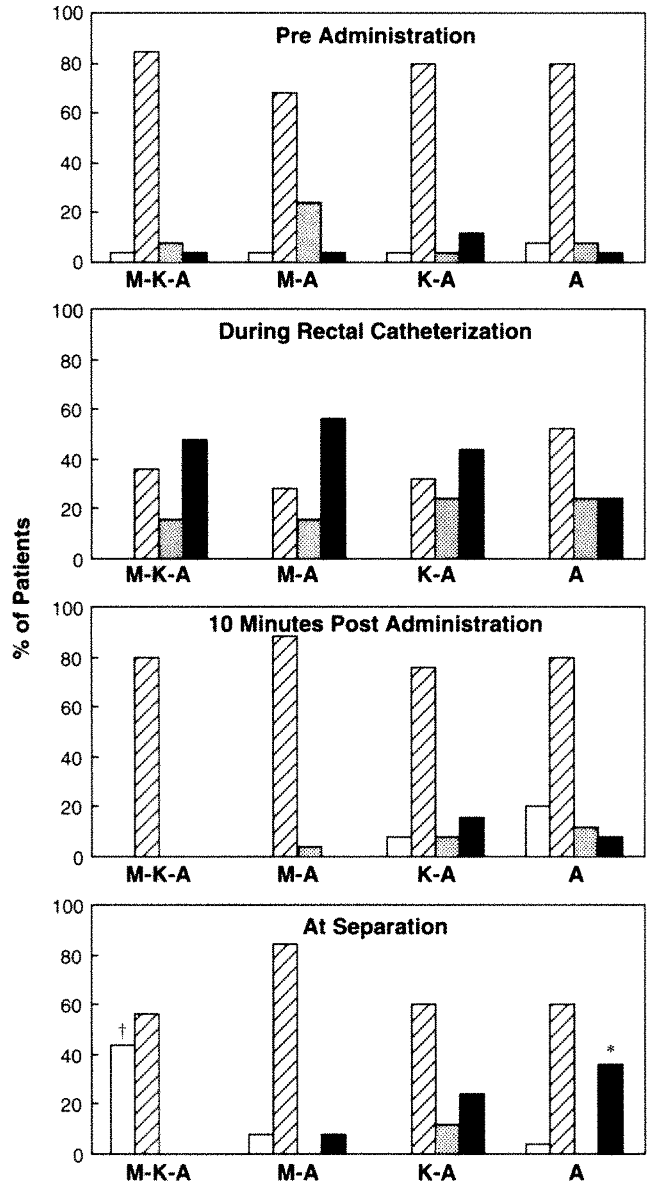

Figure 1. Percentage of patients in each sedation category before administration, during rectal catheterization, 10 min after administration, and at separation. M-K-A, midazolam (0.5 mg/kg), ketamine (3 mg/kg), and atropine (0.02 mg/kg); M-A, midazolam (0.5 mg/kg) and atropine (0.02 mg/kg); K-A, ketamine (3 mg/kg) and atropine (0.02 mg/kg); A, atropine (0.02 mg/kg). *Open bar,* asleep; *hatched bar,* calm; *stippled bar,* restless; *solid bar,* crying. *$P < 0.05$; A vs M-A or M-K-A. †$P < 0.01$; M-K-A vs M-A, K-A, or A.

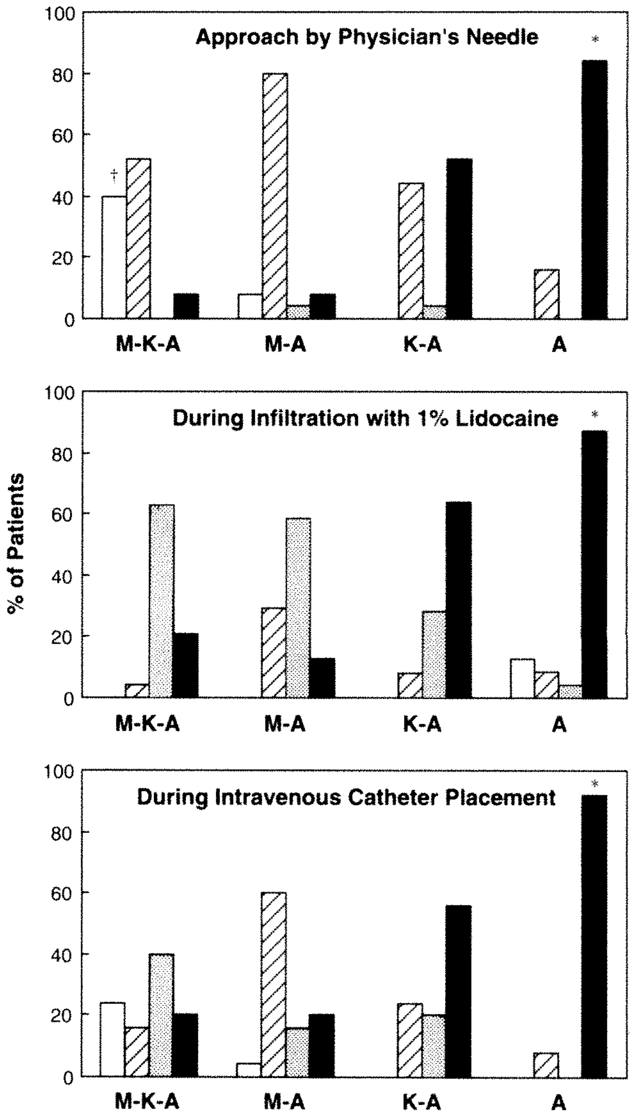

Figure 2. Percentage of patients in each response category on approach with a physician's needle, during local anesthetic infiltration, and during intravenous catheterization. Abbreviations as in Figure 1. *Open bar,* asleep; *hatched bar,* calm; *stippled bar,* withdraws but allows; *solid bar,* crying. *$P < 0.05$, A vs K-A; $P < 0.001$, A vs M-A or M-K-A. †$P < 0.05$; M-K-A vs M-A, K-A, or A.

vation (A, 0%; K-A, 8%; M-A, 0%; M-K-A, 4%), postextubation croup (A, 0%; K-A, 0%; M-A, 4%; M-K-A, 4%), or nausea and vomiting (A, 8%; K-A, 0%; M-A, 0%; M-K-A, 0%).

Eighty percent of the patients in the M-K-A group, 84% in the M-A group, 88% in the K-A group, and 80% in the A group underwent extubation in the operating room. The remainder of the patients in the M-K-A group and K-A groups underwent extubation within the first 15 min after surgery. However, in two patients in the M-A group and in one in the A group, the tracheas remained intubated beyond 30 min in the recovery room until recovery from anesthesia occurred. In addition, the trachea of one patient in the A group remained intubated overnight electively because of extensive surgery in the pharynx and concern that the airway would be compromised by early tracheal extubation.

Discharge time was prolonged in more children in the M-A group (48%) than in those who received the control solution (21%; $P < 0.05$). More children had delayed discharge in the M-K-A (40%) and K-A (24%)

groups as well, but the differences from the children who received the control solution were not statistically significant (M-K-A vs A: $0.05 < P < 0.10$; K-A vs A: P = NS). All of the children with prolonged discharge times in the M-A and M-K-A groups and 50% in the K-A and 80% in the A groups had an intravenous induction with thiopental. The mean times to discharge were also longer in the M-A (59 ± 43 min), M-K-A (51 ± 33 min), and K-A (47 ± 39 min) groups than in the children who received the control solution (40 ± 21 min), but the differences among the groups were not statistically significant.

Discussion

This study clearly demonstrated that rectally administered midazolam, with or without ketamine, facilitated IV cannulation in young children. Both the response to IV cannulation and the success rate of IV catheterization were improved in children who received midazolam or midazolam plus ketamine. In addition, this study confirmed the results of other studies of rectal sedation and showed that rectal midazolam facilitated parental separation (2,5).

Most children who received midazolam and atropine alone remained awake both during parental separation and IV cannulation. This finding was consistent with the results of a study by Spear et al. (5), which showed that doses of midazolam up to 3 mg/kg administered rectally did not produce unconsciousness in young children. In contrast, the addition of ketamine (3 mg/kg) to midazolam and atropine caused 44% of the children in our study to be asleep when separating from their parents. This may be due to an interaction of midazolam with ketamine rather than a simple additive effect, because none of the children who received ketamine and atropine alone and only 8% of those who received midazolam and atropine alone were asleep at separation.

The anesthesiologist may desire the child to be asleep during the time of parental separation, and this can be achieved with the addition of ketamine to midazolam and atropine. There also was no evidence of arterial oxygen desaturation during this period. However, when sedating an infant or young child, the anesthesiologist must have the equipment and monitoring available to manage an unconscious patient. In situations where it is desirable to have the patient awake but cooperative before the induction of general anesthesia, midazolam should be used without ketamine.

We were not, however, able to demonstrate any benefit of adding ketamine to midazolam and atropine in improving IV placement. Because most children who did not receive midazolam were crying before the lidocaine was instilled or the IV catheter was placed, anxiolysis, provided by midazolam, not analgesia, may be the important factor in aiding IV catheterization in young children.

The incidence of perioperative complications in the children who received each of the three types of rectal sedation was similar to that of the children who received the control solution. There was, however, evidence that rectal midazolam prolonged recovery time in some patients. This differed from the study by Spear et al. (5), where rectal midazolam at doses up to 1.0 mg/kg was found not to prolong recovery time in young children. However, all of the children in their study received an inhaled induction of general anesthesia with halothane and nitrous oxide rather than the IV induction with thiopental received by all of the patients in our study given rectal midazolam whose recovery times were prolonged. This suggests that rectal midazolam may interact with IV thiopental to prolong discharge time. The possibility of an interaction of midazolam with IV induction drugs or other IV agents to prolong recovery time should be considered by anesthesiologists when using rectal sedation with midazolam.

In summary, midazolam and atropine with or without ketamine aided IV catheter placement and facilitated parental separation in young children. The addition of ketamine to midazolam and atropine caused more children to be asleep. Although the rectal route of administration may cause transient distress, rectally administered midazolam and atropine with or without ketamine can be a useful combination for cooperative separation of children from their parents and for IV catheter placement before induction of general anesthesia.

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Plasma Lidocaine Concentrations During Epidural Blockade With Isoflurane or Halothane Anesthesia

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Because isoflurane maintains hepatic blood flow at higher flows than halothane, we proposed that the elimination of lidocaine would be different between these two volatile anesthetics. The plasma lidocaine concentrations were determined in 14 female patients undergoing epidural blockade plus isoflurane anesthesia and compared with those obtained during halothane anesthesia for lower abdominal surgery. General anesthesia was maintained with isoflurane (0.46% ± 0.04% [mean ± SE] inspired, $n = 7$) or halothane (0.48% ± 0.05% inspired, $n = 7$) and 67% nitrous oxide in oxygen. All patients received 2% lidocaine solution, 10 mL as a bolus dose and continuous administration at a rate of 10 mL/h, through the epidural catheter. The plasma lidocaine concentrations over 180 min after the epidural injection in patients receiving isoflurane were similar to those in patients receiving halothane. The results suggest that low inspired concentrations of isoflurane do not reduce plasma lidocaine concentrations in patients during epidural blockade, compared with halothane.

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Seventy percent of lidocaine is removed from the blood in one circulation through the liver; therefore high plasma concentrations of lidocaine are achieved in patients with a low hepatic blood flow (1). Scott et al. (2) reported that hepatic blood flow is extremely important with regard to the rate at which elimination occurs because the liver is responsible for the destruction of lidocaine.

According to several reports, isoflurane maintains hepatic blood flow and hepatic oxygen supply at higher levels than halothane (3–8), although isoflurane produces a moderate decrease in hepatic blood flow (9). A more recent clinical study demonstrated in humans anesthetized with fentanyl that hepatic blood flow increased significantly during 1.0 MAC of isoflurane but not during 1.0 MAC of halothane (10). The current clinical study was designed to compare the plasma lidocaine concentrations during epidural blockade in surgical patients anesthetized with isoflurane or halothane.

Methods

Fourteen adult female patients, ASA physical status I, ranging in age from 25 to 51 yr, scheduled to undergo epidural blockade plus general anesthesia for surgical procedures of the lower abdomen, were selected for this study. The study protocol was approved by our Institutional Human Studies Committee, and written informed consent was obtained from each patient. No patient had any hepatic, cardiopulmonary, or neurologic disorders. All patients were premedicated with oral diazepam (10 mg) and famotidine (20 mg) 90 min before arrival in the operating room. A 16-gauge intravenous catheter was placed after local infiltration of 1% mepivacaine for infusion of lactated Ringer's solution at an approximate rate of 10 $mL \cdot kg^{-1} \cdot h^{-1}$ throughout the study.

After patients were placed in the lateral ducubitus position, the skin of the lumbar region was washed with antiseptic solutions and draped, and local infiltration was performed using 1% mepivacaine (5 mL) intradermally and subcutaneously at L2-3 or L3-4 intervertebral space. A 16-gauge Tuohy needle was then introduced into the epidural space using the balloon technique. After identification of the epidural space, an epidural catheter was advanced cephalad approximately 4–5 cm into the epidural space for continuous blockade. The patient was then placed in the supine position.

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All patients were anesthetized with thiamylal (4–5 mg/kg IV), and tracheal intubation was facilitated with administration of vecuronium (~0.2 mg/kg IV). Then, general anesthesia was maintained with isoflurane or halothane (~0.5% inspired) and 67% nitrous oxide in oxygen. The inspired concentration of volatile anesthetic was adjusted to maintain small and centrally fixed pupils. The lungs were mechanically ventilated to maintain $Paco_2$ between 30 and 42 mm Hg with monitoring of end-tidal CO_2. A radial arterial cannula was placed for continuous monitoring of arterial pressure and blood sampling for measurements of plasma lidocaine concentration and arterial blood gas analyses.

Epidural anesthesia was produced by injection through the epidural catheter of 2% plain lidocaine solution (10 mL). A test dose was not used. Immediately after the initial injection, 2% plain lidocaine solution was continuously infused into the epidural space at a rate of 10 mL/h for 3 h (11,12).

Arterial blood samples for measurement of plasma lidocaine concentrations were withdrawn at 5, 10, 15, and 20 min and then at 20-min intervals after the first injection of lidocaine for 180 min. Blood samples were collected into glass tubes, centrifuged at 3000 rpm, and stored at −25°C until analyzed. The plasma lidocaine concentration was measured by homogeneous enzyme immunoassay (model aca discrete clinical analyzer, Du-Pont Company, Wilmington, Del.) (13). The coefficient for variability in this method was <6%, and the assay range was 1.0–12.0 μg/mL. This technique for lidocaine assay has been proved to be accurate, with a high degree of specificity and precision (14,15). The area under the plasma lidocaine concentration versus time curve to 180 min after epidural injection ($[AUC]_0^{180}$) for each patient was calculated using the trapezoidal rule (16).

Arterial blood gases were measured before and at 1-h intervals after the initial epidural administration of lidocaine. Electrocardiogram, radial arterial pressure, rectal temperature, and urinary volume were monitored in all patients throughout the study. Blood loss was replaced as necessary. Hypotension was defined as a decrease in systolic arterial pressure >30% of the preanesthetic value or a systolic arterial pressure of <90 mm Hg. Hypotension was treated with ephedrine (5–10 mg IV).

Values are presented as mean ±SE. Comparison of plasma lidocaine concentrations between the two groups was performed using two-way analysis of variance and Student's *t*-test; *P* values <0.05 were considered statistically significant.

Table 1. Summary of General Anesthetics, Upper Analgesic Level of Epidural Blockade, Ephedrine, Blood Loss, Urinary Output, Crystalloid Infusion, and Blood Transfusion in the Two Study Groups

	Isoflurane group (n = 7)	Halothane group (n = 7)
Inspired concentration of volatile anesthetics (%)	0.46 ± 0.04	0.48 ± 0.05
Thiamylal (mg/kg)	4.9 ± 0.1	4.7 ± 0.1
Vecuronium (mg/kg)	0.20 ± 0.01	0.21 ± 0.01
Upper analgesic level of epidural blockade (Th)	7.7 ± 0.5	7.7 ± 0.4
No. of ephedrine injections	1.5 ± 0.5	1.1 ± 0.4
Ephedrine (mg)	7.9 ± 2.9	6.4 ± 2.6
Blood loss (mL)	445 ± 145	545 ± 229
Urinary output (mL)	215 ± 40	203 ± 45
Lactated Ringer's solution ($mL \cdot kg^{-1} \cdot h^{-1}$)	11.2 ± 0.8	11.3 ± 0.8
Blood transfusion (mL)	214 ± 128	228 ± 119

Th, thoracic dermatome.

Values are mean ± SE. There are no significant differences between the two groups.

Results

There were no significant differences between the isoflurane and halothane groups in age (38 ± 3 vs 38 ± 4 yr), body weight (48 ± 3 vs 56 ± 4 kg), and height (157 ± 2 vs 157 ± 2 cm), respectively. The mean inspired concentrations of isoflurane and halothane were 0.46% ± 0.04% and 0.48% ± 0.05%, respectively (Table 1). In addition, there were no significant differences between both groups with respect to doses of general anesthetics, upper analgesic level of epidural blockade, number of ephedrine injections, dose of ephedrine, blood loss, urinary output, infusion rate of crystalloid solution, amount of transfused blood, and arterial blood gas values during the study (Tables 1 and 2).

Arterial plasma concentration of lidocaine in the isoflurane group was not different at any period up to 180 min after epidural injection of lidocaine, compared with the halothane group (Figure 1). Therefore, there was no statistically significant difference between the two groups in $[AUC]_0^{180}$ (780 ± 51 and 701 ± 41 $\mu g \cdot min \cdot mL^{-1}$, respectively, in the isoflurane and halothane groups).

No patient showed clinical signs or symptoms associated with systemic toxicity of the local anesthetics during emergence from general anesthesia. In all patients, an adequate cutaneous analgesia (thoracic dermatome >10) was confirmed by one of the authors at the end of the operation (Table 1).

Discussion

The current clinical study demonstrated that low inspired concentrations of isoflurane do not reduce plasma lidocaine concentrations during epidural an-

Table 2. Arterial Blood Gas Values Before and 1, 2, and 3 h After Epidural Injection of Lidocaine in Patients Anesthetized With Isoflurane or Halothane and Nitrous Oxide in Oxygen in the Two Study Groups

	Before lidocaine	After lidocaine		
		1 h	2 h	3 h
Isoflurane group (n = 7)				
pHa	7.42 ± 0.02	7.44 ± 0.02	7.40 ± 0.01	7.39 ± 0.02
$Paco_2$ (mm Hg)	35 ± 1	34 ± 1	37 ± 1	37 ± 1
Pao_2 (mm Hg)	160 ± 14	173 ± 12	174 ± 8	173 ± 7
Base excess (mEq/L)	−0.3 ± 0.6	−0.1 ± 0.9	−1.3 ± 0.5	−2.1 ± 0.8
Halothane group (n = 7)				
pHa	7.44 ± 0.01	7.40 ± 0.01	7.38 ± 0.01	7.38 ± 0.01
$Paco_2$ (mm Hg)	33 ± 1	37 ± 1	37 ± 1	36 ± 1
Pao_2 (mm Hg)	174 ± 11	147 ± 13	162 ± 9	162 ± 6
Base excess (mEq/L)	−0.3 ± 0.2	−1.0 ± 0.9	−2.1 ± 0.6	−2.2 ± 0.9

Values are mean ± SE. There are no significant differences between the two groups.

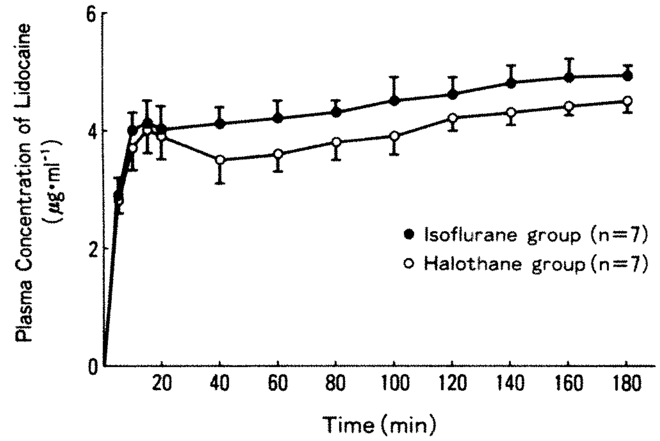

Figure 1. Plasma concentration of lidocaine after epidural injection of 2% plain lidocaine solution, 10 mL as a bolus dose, followed by a continuous infusion at 10 mL/h in patients anesthetized with isoflurane or halothane and nitrous oxide in oxygen.

esthesia in humans compared with halothane. This finding could be attributed to similar effects of low concentrations of isoflurane and halothane on hepatic blood flow in patients undergoing lower abdominal surgery under epidural plus general anesthesia.

Hepatic clearance of lidocaine is one of the major determinants of plasma concentration, because lidocaine is a drug with a high intrinsic clearance and extraction ratio; approximately 70% of lidocaine is removed from the blood reaching the liver in one circulation (1). Therefore, because its hepatic clearance is more influenced by hepatic blood flow than by hepatic enzyme activity (17,18), reductions in hepatic blood flow associated with low cardiac output have been reported to result in higher plasma lidocaine concentrations in patients with heart failure (19,20) or in animals with hypovolemia (21).

Hepatic blood flow could be disturbed primarily by the pharmacologic properties of anesthetics, their associated hemodynamic alterations, and surgical procedures during anesthesia (22). Among volatile anesthetics, isoflurane seems to have minimal deleterious effects on hepatic circulation, evidenced by previous animal and human investigations (3–8,10). Indeed, equal degrees of arterial hypotension have been demonstrated to be accompanied by pronounced reduction in hepatic blood flow during halothane anesthesia but not during isoflurane anesthesia (3–8). However, there are few data concerning the effects of low concentrations of volatile anesthetics (<1.0 MAC) on hepatic blood flow.

Gelman (23) and Bohrer et al. (24) described the importance of surgical stress-induced derangements in hepatic blood flow. According to their extensive works on hepatic circulation, surgical stress should have a profound influence on the hepatic blood supply. Laparotomy as a surgical stress is indeed associated with mesenteric vasoconstriction and the release of vasoactive substances that could disturb the hepatic circulation (25–27). More important, these derangements are reported to persist for several hours. However, epidural blockade could have alleviated these surgical stress responses to a great extent in the present study.

Therefore, no difference in plasma lidocaine concentrations over 180 min between the isoflurane and halothane anesthesia groups in the present study (Figure 1) could be attributed to comparable effects of low concentrations of both volatile anesthetics on hepatic circulation. Because hypotension was treated immediately with ephedrine, and numbers of hypotensive episodes and the mean total administered doses of ephedrine were comparable between the two groups (Table 1), it appears that anesthesia-induced systemic hemodynamic alterations were clinically similar between the isoflurane and halothane anesthesia groups. Likewise, the effects of isoflurane and halothane at the low concentrations used during the current study may also not produce differences in hepatic circulation between the two groups, because Gelman et al. (3) emphasized that anesthetics may only modulate the hemodynamic alterations in the liver induced by surgical stress. Furthermore, because isoflurane has a more potent vasodilating action than halothane in humans (28,29), no difference in plasma lidocaine concentrations may be due to the fact that increased absorption of lidocaine through the epidural vessels would have masked the accelerated hepatic uptake of lidocaine during isoflurane anesthesia.

In conclusion, low concentrations of isoflurane do not reduce plasma lidocaine concentrations during epidural anesthesia in patients undergoing lower abdominal surgery compared with halothane. This finding may be due to similar effects of low concentrations of volatile anesthetics on hepatic blood flow during epidural blockade.

We thank Mrs. Y. Isaka for her help in the measurement of plasma lidocaine concentrations.

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A Rat Sciatic Nerve Model for Independent Assessment of Sensory and Motor Block Induced by Local Anesthetics

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The purpose of this study was to develop a reliable model to independently quantify motor and sensory block produced by local anesthetics. The sciatic nerve was blocked in 52 rats by injecting 0.2 mL of 0.125%, 0.25%, 0.5%, or 0.75% bupivacaine (n = 13 for each concentration). Accurate needle placement was achieved using a nerve stimulator at 0.2 mA and 1 Hz. Ten control rats received 0.9% saline (n = 5) or sham nerve stimulation (n = 5). Motor block was assessed by measuring hindpaw grip strength with a dynamometer. Sensory block was determined by measuring hindpaw withdrawal latency from radiant heat. The intensity of both motor and sensory block measured at 30-min intervals was plotted against time until full recovery to obtain the area under the curve. Intergroup comparisons using analysis of variance showed increasing area under the curve with increasing concentrations of bupivacaine for motor blocks ($P < 0.05$ for all intergroup comparisons except 0.5% vs 0.75%) and sensory blocks ($P < 0.05$ for all intergroup comparisons). Normal saline or sham nerve stimulation did not result in any motor or sensory block.

(Anesth Analg 1992;75:889–94)

Several investigators have used in vivo animal models to evaluate local anesthetic-induced conduction block. The sciatic nerve block has been used in the guinea pig (1–4) and rat (5–12); spinal block in sheep (13), monkey (14), dog (10,15–18), rabbit (2,3,7,19–22), rat (23–26), mouse (25,27), and marmoset (23); and epidural block in the dog (10,28), cat (29), rat (30), and marmoset (23). Although some of these studies reported motor as well as sensory effects of local anesthetics, none quantified both variables objectively. All studies used visual observation to grade motor block. The presence of sensory anesthesia was tested by eliciting vocalization, withdrawal, or respiratory response to pinprick, heat, or pressure stimulus. In addition, all reported sciatic nerve block models used blind percutaneous injections, except one in which a silicone sheath was surgically implanted around the sciatic nerve (12).

We present a model of percutaneous sciatic nerve block in the rat using a nerve stimulator to locate the sciatic nerve accurately. Modification of a technique to measure grip strength (31) enabled us to quantify intensity and duration of unilateral grip strength objectively. We measured paw withdrawal latency from radiant heat stimulation (5,32,33) to quantify the intensity and duration of unilateral sensory anesthesia.

Methods

All experiments were approved by the Institutional Animal Care and Use Committee and conducted in accordance with their guidelines.

Percutaneous Rat Sciatic Nerve Model

Male Sprague-Dawley rats (Taconic Farms, Pa.) (365 ± 26 g [mean ± SD], range 345–410) were housed five per cage in a room with controlled environmental temperature, humidity, and artificial lighting (7 AM–8 PM). The animals had free access to food and water and were not tested for at least 10 days after their arrival from the supplier.

All animals were anesthetized by placing them in a chamber flushed with 5% halothane in oxygen at a rate of 2 L/min for 5 min. The animals were then removed from the chamber and allowed to breathe room air. After being placed on their left side, the groove between the greater trochanter of the right

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femur and the ischial tuberosity was identified by palpation. A 24-gauge 45° beveled Teflon-shielded needle (Stimuplex, B. Braun, Melsungen, Germany) attached to a nerve stimulator (DigiStim II, Neuro-Technology, Houston, Tex.) was advanced into the groove while being stimulated at 1 Hz. A pilot study of 15 rats showed the minimal effective current required to produce twitch with the needle tip directly on the surgically exposed sciatic nerve to be 0.2 mA. It has been shown that direct current stimulation of the rat sciatic nerve using 0.5 mA does not cause neuropathologic changes (34). Close proximity of the needle tip to the sciatic nerve during percutaneous blocks was confirmed by a noticeable twitch of the hindpaw at a stimulus intensity ≤0.2 mA. While the operator held the needle steady, an assistant activated a Harvard infusion pump to inject 0.2 mL of the test solution at a constant rate of 1.2 mL/min through a catheter attached to the needle. All animals were returned to their cages to recover from anesthesia after the injection was completed.

Assessment of Motor Block

We modified an apparatus described for measuring bilateral grip strength (31) to measure unilateral hindpaw grip strength after the sciatic nerve block. The modified device consists of a horizontally mounted, 6-mm mesh stainless steel screen attached to an electronic force-gauge dynamometer (model DFGHS2, Chatillon, Greensboro, N.C.) that samples at a rate of 4500/s and updates the digital display 15 times per second. Rats were positioned on a plexiglass bench adjacent to the screen so that the two forelimbs and the normal hindlimb rested on the bench and the blocked hindlimb rested on the screen.

For each test, the rat's tail was pulled backward in a smooth but firm manner until the rat's grip on the screen was broken. The dynamometer registered peak grip strength in grams. The strongest response of three consecutive attempts was used for statistical analysis. Baseline grip strength was measured by a blinded operator before the sciatic nerve block and again every 30 min after the block until return to baseline grip strength.

Assessment of Sensory Block

Sensory anesthesia of the plantar surface of the paw was determined using unilateral hindpaw withdrawal latency (PWL) to radiant heat stimulation (32,33,35). Rats were placed in bottomless, clear plexiglass rectangular chambers (12 × 16 × 30 cm high) on a glass shelf (2 mm thick) and allowed to acclimate to their surroundings for 5 min. The surface temperature of the shelf was measured with a thermistor monitor (Mon-a-therm, model 4070, Mallinckrodt, St. Louis, Mo.). The surface of the glass shelf was maintained at a constant temperature between 27.5 and 28.5°C using a warm-air blower situated below. A movable radiant heat source (tungsten halogen projector lamp, 150 W, 100 V, GTE, Winchester, Ky.) powered by a constant current supply was focused on the glass from below through a 4-mm-diameter aperture. A single switch activated both the radiant heat source and an electronic timer capable of measuring 0.1-s intervals. In a series of experiments, the distance from lamp to glass and initial temperature of the glass shelf were adjusted by trial and error to yield a mean PWL of 5.2 ± 0.6 s.

After the animal settled in place on the glass shelf, the heat source was positioned under the plantar surface of the desired hindpaw, assuring that the plantar skin was in contact with the glass. The heat source was turned on until the hindlimb was briskly withdrawn from the glass shelf. Average baseline PWL was determined in triplicate for the entire study group. For PWL testing, a cutoff time of 10 s was used to avoid thermal injury (erythema, edema, or blistering). However, in pilot studies, repeated PWL testing (more than eight times) to cutoff time (10 s) in paralyzed paws sometimes resulted in thermal injury. Additionally, in pilot studies, we found that every animal with complete motor block as evidenced by a clubbed paw had maximal PWL. Thus, we decided to assess PWL only when complete motor paralysis was not present.

Experimental Design

Sixty-two rats were divided into six groups. Rats in groups I–IV ($n = 13$ per group) were injected with 0.2 mL of 0.125% bupivacaine (group I), 0.25% bupivacaine (group II), 0.5% bupivacaine (group III), or 0.75% bupivacaine (group IV) (Marcaine HCl, Winthrop Pharmaceuticals, New York, N.Y.). The pH of the commercially prepared solutions was 5.9, 5.8, and 5.5 for 0.25%, 0.5%, and 0.75% solutions, respectively. The 0.125% solution was prepared by diluting 0.25% bupivacaine with 0.9% saline and adjusting the final pH to 5.9 using 1 M NaOH. Group V ($n = 5$) was injected with 0.2 mL of 0.9% saline (pH 5.4), and group VI ($n = 5$) had nerve stimulation alone, without any solution injected.

After injection (or nerve stimulation alone), motor block was measured by a blinded observer every 30 min. Nerve block was deemed successful if complete motor block was present at 30 min. Failure to grip the screen and complete clubbing of the hindpaw was indicative of complete motor block. Animals in groups I–IV that did not develop complete clubbing were not included for statistical analysis (10).

Grip-strength testing was performed at 30-min intervals after the block, and once the rat regained the ability to grip the screen, PWL testing was also performed at 30-min intervals. Both grip strength and PWL testing were continued every 30 min until return to baseline. Hindpaws were visually inspected for erythema, edema, or blistering at the end of each experiment.

Data Analysis and Statistics

Intensity of motor block was determined at each time interval for each rat by computing percent of preinjection grip strength. Intensity of sensory block was calculated for each rat at each time interval by determining percent maximal possible effect (% MPE), according to the following formula:

$$\% \text{ MPE} = \frac{\text{Postinjection latency} - \text{Preinjection latency}}{\text{Cutoff time (10 s)} - \text{Preinjection latency}} \times 100.$$

The percent motor block and percent MPE were plotted against time to determine the area under the curve (AUC) using the linear trapezoidal method (36,37). Results were expressed as mean ± SD. Differences in motor or sensory block produced by each bupivacaine concentration were compared using their respective AUCs. For statistical comparison, analysis of variance was used. If a significant F value ($P < 0.05$) was seen with analysis of variance, a protected least-significant difference test was used to make intergroup comparisons (38) using Complete Statistical Systems software (StatSoft, Tulsa, Okla.).

Results

At 30 min, 12 of 13 (92%) of the rats in groups I, II, and IV had complete clubbed paw; thus, 1 rat from each of these groups was eliminated from the study. All rats in group III had complete clubbed paw. No group V or VI rat had clubbing at any time. No intergroup differences existed for frequency of blocks among groups I–IV, all of which differed significantly from groups V and VI.

Mean baseline hindpaw grip strength was 649 ± 89 g. In groups I–IV, the intensity and duration of motor block increased with increasing bupivacaine concentration (Figure 1); 0.5% bupivacaine produced a greater AUC than 0.125% or 0.25% ($P < 0.05$) but an AUC similar to that produced by 0.75% bupivacaine (Figure 2). No group V or VI animal had a decrease in grip strength from baseline. Both groups were significantly different from groups I–IV but not from one another.

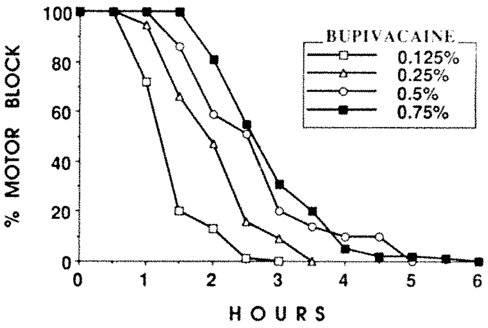

Figure 1. Mean duration of motor block for various concentrations of bupivacaine, as measured by grip strength. Percent motor block was calculated as 1 − (postblock grip strength/preblock grip strength) × 100. Time 0 represents the first testing interval. For clarity, standard deviations are not shown.

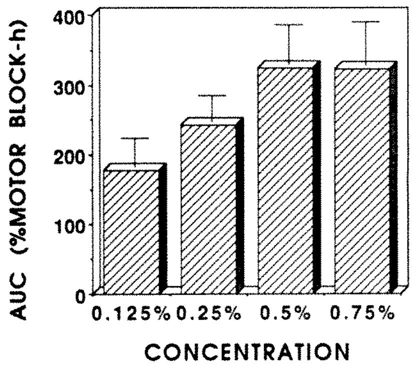

Figure 2. Total area under the curve (AUC) for motor block produced by various concentrations of bupivacaine. All intergroup comparisons significantly different, except 0.5% versus 0.75%.

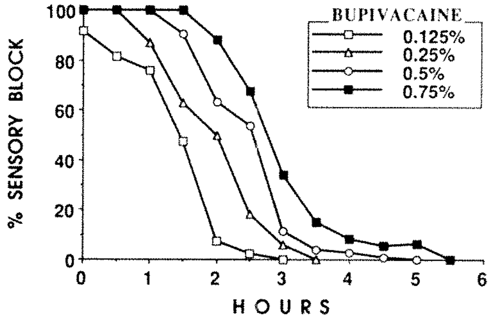

Figure 3. Mean duration of sensory block for various concentrations of bupivacaine, as measured by paw withdrawal latency. Percent maximal possible effect was calculated as explained in text. Time 0 represents the first testing interval. For clarity, standard deviations are not shown.

The mean preblock PWL was 5.0 ± 0.5 s. The mean PWL for all rats fell within 2 SD of the mean for the entire group. The intensity and duration of sensory block increased with increasing concentration of bupivacaine (Figure 3). Increasing concentration of bupivacaine produced increasing AUC ($P < 0.05$) for all intergroup comparisons (Figure 4). No animal in groups V or VI had sensory block. No rat had erythema, edema, or blistering of the hindpaw.

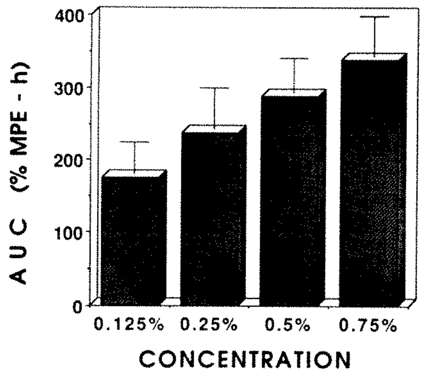

Figure 4. Total area under the curve (AUC) for sensory block produced by various concentrations of bupivacaine. All intergroup comparisons significantly different. % MPE, percent maximal effect.

Discussion

We describe here a percutaneous rat sciatic nerve block model that allowed us to independently quantify motor and sensory block produced by various concentrations of bupivacaine.

Sciatic Nerve Model

The sciatic nerve block model for evaluation of local anesthetic action was first described in the guinea pig in 1935 (1) and later used by others (2–4). A rat sciatic nerve model was described in 1958 (5). We found no subsequent reports using the guinea pig model, perhaps because the rat's natural posture makes motor block easier to evaluate (5). The original rat sciatic nerve block used a tuberculin syringe fitted with a 26-gauge needle to inject the popliteal space (5). Although other reports use more proximal injection sites (6–9,11,12), a recent study used the popliteal approach to inject 0.1 mL of local anesthetic in 450–600-g rats (10). The others used 0.2–0.25 mL of local anesthetic in 130–250-g rats (6–9,11). A conventional needle-syringe arrangement was utilized in all of these studies. Recently, a silicone sheath was surgically implanted around the sciatic nerve to permit multiple local anesthetic injections through a subcutaneous port to study neurotoxic effects (12).

We believe that the method we describe is superior to previously described models. The uncertainties of blind injection are avoided by using nerve stimulation to locate the nerve precisely. Although this is not a new technique for ensuring proper needle placement (39), we can find no use of it reported for these purposes. The block can usually be performed in <2 min by using the greater femoral trochanter and the ischial tuberosity as landmarks. The injected volume of 0.2 mL is consistent with the volume used in previous reports (6–9,11), although our rats were larger. The immobile needle technique (40) maximizes injection accuracy. Nerve stimulation-guided needle placement in conjunction with an automated infusion pump ensures a standard rate of injection and consistently results in a high success rate (94%).

Evaluation of Motor Block

Evaluation of sciatic motor block in the rat induced by injected local anesthetic has previously been based on semiquantitative observations of such variables as ability of the rat to negotiate an inclined wire mesh or on observation of the rats' posture and degree of apposition of the hindpaw digits (5–12,26,30). One investigator did attempt to quantify hindpaw motor function after injury of sciatic nerves (41). Rats were allowed to walk over photographic paper after the hindpaws were painted with photographic developer. The hindpaw imprints were then analyzed, and an index of motor function was derived.

We measured unilateral hindpaw grip strength based on a device recently described using a screen attached to an electronic dynamometer to assess bilateral hindpaw grip strength in the rat (31). We modified this device to allow testing of unilateral hindpaw grip strength by extending the forepaw platform rest to include the unblocked hindpaw as well. This left only the blocked hindpaw in contact with the screen.

Testing at 30-min intervals allowed measurement of duration and intensity of motor block. By then plotting the percent of baseline block for each time interval for every rat, we were able to calculate the AUC for each rat and to make intergroup comparisons of total AUC using analysis of variance.

We believe that the simplicity, reliability, and precision of this method makes it clearly superior to previously reported methods to measure intensity and duration of motor block.

Evaluation of Sensory Block

Some in vivo animal studies of local anesthetic conduction block have assessed sensory loss using nonquantitative methods (3,4,19,23). We have found no study reporting assessment of sensory anesthesia after rat sciatic nerve block. We used a radiant heat source to evaluate sensory anesthesia, applying recently described technology for measuring cutaneous hindpaw anesthesia in the rat (5,32,33).

Analgesia tests in the rat using thermal stimulation (tail flick, hot plate) have been used for 50 yr (42,43). These tests are useful for evaluation of systemic or neuraxial analgesics but have limited application for local anesthetics, because they cannot clearly differentiate between motor and sensory block. Also, utility of the tail-flick test to predict clinical action of local anesthetics is unclear, because intrathecal or epidural injections in the rat and mouse have been reported to result in a hyperreflexive tail-flick response (24, 25,30). Hot-plate testing to evaluate effects of local anesthetics has also been reported (27,30); however, like the tail-flick test, it cannot be used for unilateral testing.

An advantage of the thermal stimulation system described here is that a unilateral hindpaw can be tested. This allows the animal's unblocked other paw to serve as a control. Another significant advantage of this model is that it permits independent motor and sensory testing. A rat with complete motor block but incomplete sensory block still can withdraw its paw, because the hip muscles not innervated by the sciatic nerve allow withdrawal from the heated glass. It may be important to assess differential anesthetic effects on motor and sensory block, especially because injection of neurotoxic substances may cause prolonged motor block with little or no sensory loss or hyperesthesia.

In preliminary studies, we, like other investigators (33,44), found that baseline PWL was inversely related to the initial temperature of the glass shelf surface. This was nullified by controlling the shelf surface to a measured temperature of 27.5–28.5°C by heating with a hot-air blower beneath the shelf or cooling its surface with a damp sponge. Baseline PWL values were very consistent so long as temperature was controlled. This consistency in PWL also allowed us to use a 10-s cutoff time to calculate percent MPE and AUC.

To avoid the possibility of heat stimulation beyond the desired paw surface area, we used an aperture diameter of 4 mm and took particular care to stimulate only hindpaw skin in direct contact with the glass surface (33,45,46). Tissue injury is a potential pitfall of any thermal testing system. We did not begin to measure PWL until motor block regressed enough to permit paw motion. This avoided unnecessary hindpaw heating for the maximal (cutoff) time of 10 s.

Conclusion

The percutaneous rat sciatic model we describe here allowed us to independently assess motor and sensory block produced by various concentrations of bupivacaine. The nerve stimulator enabled us to perform the blocks easily without surgery and to achieve a high rate of success. The grip strength and PWL tests allowed us to accurately quantify degree of block. The sensitivity of these tests allowed detection of even small degrees of block and discriminated among different concentrations of local anesthetic. This method may be useful for evaluation of local anesthetics.

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Lumbar Subarachnoid Ethylenediaminetetraacetate Induces Hindlimb Tetanic Contractions in Rats: Prevention by $CaCl_2$ Pretreatment; Observation of Spinal Nerve Root Degeneration

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Disodium ethylenediaminetetraacetate (Na_2EDTA) has replaced sodium bisulfite as the antioxidant in 2-chloroprocaine, Nesacaine CE. This study was undertaken to determine whether this new formulation has neurotoxic effects when administered in the subarachnoid space. Sprague-Dawley rats receiving subarachnoid injections of 1.5 mM or higher concentrations of Na_2EDTA immediately initiated a circling behavior that was followed by the development of tetanic contractions of the hindlimbs lasting for 15–20 min. The tetanic contractions were followed by a brief period of hindlimb paralysis. Pretreatment of rats by subarachnoid injections of 1 mM $CaCl_2$ prevented the development of tetanic contractions and paralysis of the hindlimb. Histologic examination of animals receiving Na_2EDTA revealed moderate to severe focal degenerative changes in spinal nerve roots. Control rats receiving subarachnoid injections of normal saline solution did not develop tetanic contraction nor pathological changes on light microscopy. These results suggest that the preservative used in Nesacaine-MPF may be neurotoxic.

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Sodium bisulfite, an antioxidant contained in 2-chloroprocaine, Nesacaine CE, has recently been replaced by a chelator, disodium ethylenediaminetetraacetate (EDTA) dihydrate. A number of adverse effects have been reported after enteral and parenteral administration of EDTA. These include teratogenicity (1); collagen fibril depletion (2); intestinal villi shortening (3); neural crest tumor formation and cell death in rats and mice (4); hepatic necrosis in calves (5); and contact allergy (6), vasculitis, cardiac tamponade, hemolytic anemia, and renal damage in humans (7). Moreover, systemic hypocalcemia and increased parathyroid hormone have been reported in humans after radiography with contrast media containing EDTA (8). Use of this type of contrast for coronary angiography has also caused ventricular fibrillation and repolarization changes (9). Ethylenediaminetetraacetate containing 2-chloroprocaine-MPF has been used widely as an epidural anesthetic and may enter the subarachnoid space through accidental dural puncture. The effects of EDTA in the subarachnoid space are unknown. A rat model was used to test the effects of EDTA in the subarachnoid space.

Methods

With approval of our Animal Care and Research Committee, Sprague-Dawley rats weighing 500–600 g were anesthetized with 0.5 mL/kg intramuscular injection of an anesthetic mixture that contained ketamine (42.85 mg/mL), xylazine (8.57 mg/mL), and acepromazine (1.42 mg/mL). After lumbar laminectomy, with aseptic technique, PE10 subarachnoid space (SAS) catheters (Becton Dickinson, Parsippany, N.J.) were implanted under direct vision with a technique recently reported (10). One week after surgery, correct position of the SAS catheter was verified by observing temporary hindlimb paralysis after induction of spinal block with 0.05 mL of 1.5% lidocaine. One or more days after this test, the animals were divided into five groups receiving SAS injections at 1-h intervals, as follows: group 1 (control

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Table 1. Occurrence of Tetanic Contractions After Subarachnoid Injections of Different Concentrations of Na_2EDTA in Rats

	Na_2EDTA			
Rat No.	0.01%	0.025%	0.05%	0.1%
1	NE	NE	NE	NE
2	NE	NE	3rd	2nd
3	NE	NE	2nd	1st
4	NE	NE	NE	1st
5	NE	NE	NE	1st
6	NE	NE	1st	1st

EDTA, ethylenediaminetetraacetate; NE, no effect (no tetanic contraction); 1st, 2nd, 3rd, injection number when tetanic contractions were observed.

animals, $n = 6$) received three SAS injections (at 1-h intervals) of normal saline solution (NS) (50 μL [0.05 mL], pH 5). Group 2 (EDTA only, $n = 6$) received (at 1-h intervals) three to four SAS injections of 0.05 mL of Na_2EDTA (molecular weight 336.21, pH 4.5–4.8) of varied concentrations on different days, including 0.01% (0.3 mM), 0.025% (0.75 mM), 0.05% (1.5 mM), and 0.1% (3 mM). Group 3 ($CaCl_2$ + Na_2EDTA, $n = 7$), at 1-h intervals, received three SAS injections of 148 μL of 1 mM (0.01%) $CaCl_2$ (molecular weight 110.99, pH 5–5.7), which was immediately followed by 148 μL of 3 mM (0.1%) Na_2EDTA. Additionally, at 1-h intervals, two other rats received the $CaCl_2$ + EDTA combination six times. Group 4 (histologic study, $n = 3$ [not counting the rat from group 2]) received eight injections of 0.05 mL of 0.1% Na_2EDTA at 1-h intervals and were killed 3 days later for pathological examination of the spinal cords. Group 5 (additional histologic study of saline solution control animals, $n = 6$) received 0.05 mL of NS at 1-h intervals for 8 h and were killed 5 days later for pathological examination.

Results

There was no demonstrable motor abnormality after SAS injection of NS and 0.01% and 0.025% Na_2EDTA. One minute after 0.1% Na_2EDTA injection, five of six rats in group 2 circled around continuously and then developed tetanic contractions of the hindlimbs at a frequency of 100+/min. Four animals manifested this behavior after the first injection and one after the second injection. Three rats developed tetanic contractions of hindlimbs after 0.05% Na_2EDTA injection: one after the first, one after the second, and one after the third injection. Hindlimb paralysis lasting 10–15 min usually followed the tetanic contractions. Table 1 summarizes the results in group 2. Tetanic contractions and other motor abnormalities were not seen in group 3 rats when SAS Na_2EDTA injections were preceded by $CaCl_2$. Tetanic contractions developed in all of the group 4 animals between the fourth and eighth injections.

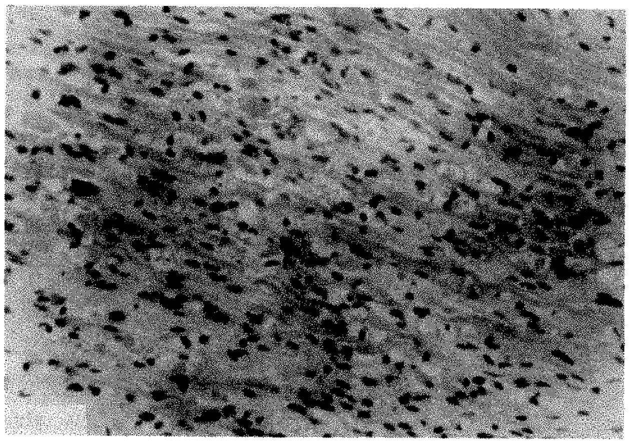

Figure 1. Low-power magnification (×25) of hematoxylin-eosin-stained section of rat spinal nerve root 6 days after receiving subarachnoid injection of Na_2EDTA. Approximately one-third of the fibers show acute vacuolar and granular degeneration. A relatively intact portion of the root is shown in the *right upper corner.*

Pathological examinations were performed in 10 animals: one from group 2, three from group 4, and six from group 5. The animal from group 2 was killed for histologic examination 6 days after receiving SAS Na_2EDTA injection every hour for 3 h. This rat had tetanic contractions after receiving the second and third SAS injections containing 0.1% and 0.05% Na_2EDTA, respectively. Before autopsy, this rat had already recovered from hindlimb paralysis and showed no sign of motor abnormality. Histologic examination revealed focal lesions characterized by destruction of axons and their myelin sheaths, resulting in cystic degeneration of nerve roots. Prominent macrophage activity was evident (Figures 1 and 2). The spinal cords of two of the three animals in group 4 revealed Wallerian degeneration of spinal nerve roots (Figures 3 and 4). In the histologic sections examined, the remaining rat in group 4 did not show degenerative changes. The spinal cord and spinal roots of group 5 rats did not show pathological changes after SAS injection of NS. There were no tetanic contractions in group 5.

Discussion

Before the formulation change, Chloroprocaine CE, Nesacaine CE contained 0.2% sodium bisulfite, which was shown to be neurotoxic in rabbits (11–13) and rats (14). Subsequently, the manufacturer reduced the antioxidant content to 0.07% and eventu-

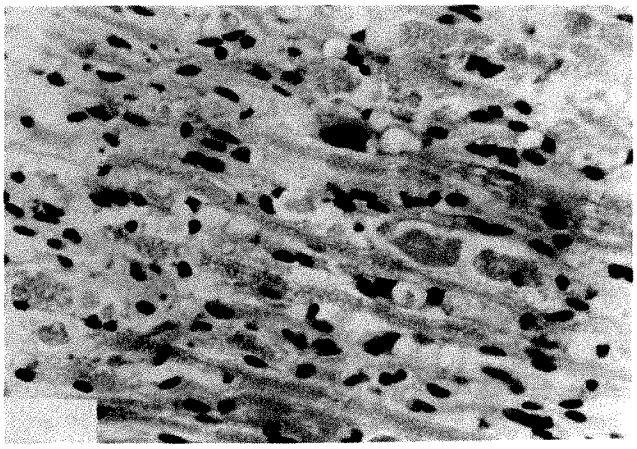

Figure 2. High-power magnification (×90) of Figure 1 showing focal lesions characterized by destruction of axons and their myelin sheaths, resulting in vacuolar and granular degeneration. Prominent macrophage activity was evident. Hematoxylin-eosin stain.

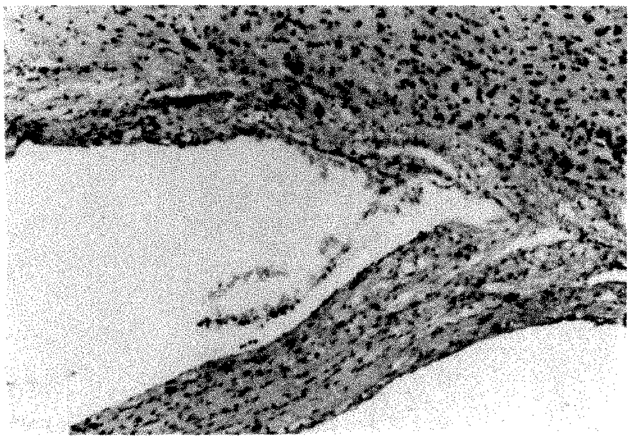

Figure 3. Spinal cord (*top*) and spinal nerve root (*bottom*) of rat 3 days after intrathecal administration of Na_2EDTA. There is multifocal degeneration of nerve root fibers characterized by formation of vacuoles containing fragments of axons and myelin sheaths. Hematoxylin-eosin stain, ×25.

ally eliminated it altogether, replacing it with EDTA. Recent reports of severe back pain after epidural chloroprocaine (Nesacaine-MPF) prompted the authors to examine the effects of EDTA in the SAS to determine if the new formulation of chloroprocaine is appropriate. We did not pinpoint the etiology of the back pain but were led to believe that EDTA is the possible cause by the following findings: (a) SAS administration of EDTA induced tetanic contractions, probably as a result of hypocalcemia; (b) $CaCl_2$ pretreatment prevented the development of tetanic contractions; (c) microscopic evidence of spinal nerve root degeneration was observed, a condition that may be associated with nerve root irritation causing pain. These three findings are discussed next.

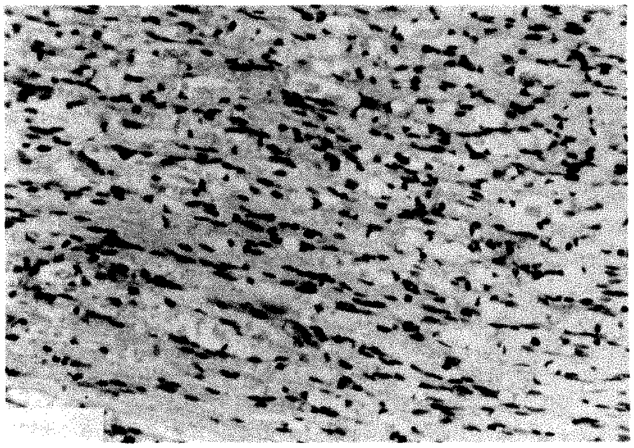

Figure 4. Spinal nerve root 3 days after intrathecal administration of Na_2EDTA. There is diffuse Wallerian degeneration of individual nerve fibers characterized by formation of vacuoles containing fragments of axons and myelin sheaths. Hematoxylin-eosin stain, ×50.

Tetanic Contractions

The fact that low concentrations (0.01% and 0.025%) of Na_2EDTA did not cause tetanic contractions indicates a concentration-dependent effect. As shown in Table 1, four rats developed tetanic contractions after the first injection of 0.1% EDTA, whereas with 0.05% EDTA, only one developed tetanic contractions after the first injection, one after the second, and one after the third. This would suggest that cumulative dosage and duration of contact may influence the result.

Because the SAS of the rat is very small, the volume of the injectate has to be limited. For this reason, we had to use concentrations of EDTA higher than the 0.011% contained in the commercial solution of chloroprocaine-MPF; however, in terms of total milligrams, the dose that we used was still only approximately 1/40 of the amount of EDTA contained in a single epidural dose of chloroprocaine-MPF in humans. In general, based on body weight, drug dosage for rats is usually much larger than that for humans.

Ethylenediaminetetraacetate chelates calcium, which plays an important role in neuromuscular function, including repolarization of the myocardium (9). Hypocalcemia causes tetany; however, the exact mechanism for the production of tetanic contraction after SAS EDTA administration remains unresolved.

In a previous study (15), tetanic contractions were also produced by EDTA administered in the epidural space. As expected, the latency period before the development of tetanic contractions after epidural EDTA was longer than that after SAS injection, because it takes time to pass through the dura.

Calcium Chloride Pretreatment

The fact that pretreatment with $CaCl_2$ prevented the development of tetanic contractions in group 3 suggests that hypocalcemia secondary to chelation could be the responsible factor. The preventive role of $CaCl_2$ was further supported by the fact that the two additional rats in group 3 did not develop tetanic contractions even after receiving, at 1-h intervals, eight injections of the combination of $CaCl_2$ + EDTA. The report of successful treatment of severe back pain after epidural Nesacaine-MPF with $CaCl_2$ (16) reinforced this support.

Patients with parathyroid hormone deficiency, impaired calcitriol synthesis, hypomagnesemia and hypermagnesemia, and diseases of the kidneys and liver are especially at risk for hypocalcemia (17). Vitamin D is synthesized in the skin or absorbed by the gut, 25-hydroxylated in the liver, and then 1-hydroxylated in the kidneys to its most active form, calcitriol. Therefore, diseases of the kidneys or liver could impair calcium homeostasis, and in patients with such ailments even a low concentration of EDTA may be unsafe.

Myoclonic seizures, probably secondary to increased serotonergic activity in the spinal cord, have been reported in rats after a tenfold analgesic dose of intrathecal morphine. This effect was reduced by pretreatment with parachlorophenylalanine in doses that reduced spinal 5-hydroxytryptamine (serotonin) by approximately 60% (18). Speculatively, if EDTA produces tetanic contractions by acting on the serotonergic pathway in the spinal cord, it would be inadvisable to add EDTA to intrathecal morphine preparations.

Opioid receptors may be affected by EDTA through calcium modulation. The binding of opioid receptors is affected by the valence of the cation (i.e., monovalent or divalent) and the site of binding (i.e., μ, δ, κ). In membrane suspensions from guinea pig brain or cerebellum, Paterson et al. (19) found that $CaCl_2$ inhibited equilibrium binding at μ and κ sites but potentiated binding at δ sites. Kappa receptors have been linked to direct blockade of the calcium channel (19). The κ-ligand dynorphin A decreases basal free intracellular calcium in rat cortical synaptosomes.

Through calcium modulation, EDTA may affect the calcium channel (20), the secondary messenger, the muscarinic receptor (21), and the acetylcholine and norepinephrine neurotransmitter release (22,23). There is evidence suggesting that leucine enkephalin and acetylcholine are cotransmitters stored in and released from the same nerve terminals in the parasympathetic ganglia of the bladder (24).

Degeneration of the Spinal Nerve Roots

Our preliminary observation that spinal nerve roots had degenerated lends support to similar results from previous investigations of epidural and SAS administration of EDTA (15,25). This would suggest that the reported severe back pain after epidural chloroprocaine-MPF (16,26–30) could be due to spinal nerve root irritation caused by EDTA contained in the anesthetic solution. Unfortunately, we did not perform pathological studies on all of our animals. Further research, including studies of Nesacaine-MPF, are warranted.

Recently, on the basis of autopsy findings in 15 patients, without substantiating evidence, Sjoberg et al. (31) have tried to exonerate low-concentration sodium metabisulfite and EDTA from causing neurotoxicity. We commend their efforts in the study but disagree with their interpretation of results. Their table of "Pathoanatomic findings" listed several patients with neurilemoma, loss of axon, demyelination of spinal nerve roots, 10 patients with "puzzling" mononuclear infiltration ("five had radiotherapy of the spinal column and three had potentially neurotoxic cytostatic treatment"), one patient with degeneration of the dorsal column and dorsal horns with focal subpial vacuolization and demyelination at the level of a neurilemoma, and one patient with arterial thrombosis and medullary infarction of the spinal cord. One patient developed paraplegia and urinary retention 158 days after the start of the intrathecal treatment, and the authors called this "an expected consequence of large daily dose (7–10 mg/h) of intrathecal bupivacaine given to cope with severe neurogenic pains." They claim that "the incidence and extent of the microscopic nerve root lesion were not related to the concentrations and cumulative doses of morphine (and its preservatives) or bupivacaine, the osmolarity and pH of the analgesic mixture, or the duration of treatment." It appears that they attribute the pathological lesions to tumor invasion, radiation therapy, and treatment with potential neurotoxic agents. Without a control study for substantiation, it would be inappropriate to make such claims that might lead medical professionals to disregard the potential toxicity of bisulfite and EDTA. We have observed nearly all these focal pathological findings in our animal models with use of EDTA (15,25) in the absence of tumor invasion, irradiation, or treatment with neurotoxic agents (Figures 1–4). Irreversible hindlimb paralysis has also been reported after intrathecal bisulfite administration in rabbits (11).

We do not assume that preservatives are responsible for all of the lesions described by Sjoberg et al. (31), but we cannot rule out EDTA and bisulfite as the cause of pathology in some of the patients. Accidental dural puncture, although rare, can be a nuisance in epidural anesthesia. Drugs intended for epidural administration could inadvertently enter the SAS. Therefore, incorporating EDTA in epidural anesthetics may be unwise before its safety is proved. Moreover, the fact that the cases of severe back pain were reported after epidural anesthesia with chloroprocaine containing EDTA suggests that complications can occur even without dural puncture.

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Prolongation of Epidural Anesthesia Using a Lipid Drug Carrier With Procaine, Lidocaine, and Tetracaine

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This study evaluated the effect of a lipid drug carrier (iophendylate) on epidural anesthesia. The intensity and duration of motor blockade produced by aqueous and lipid preparations of local anesthetics were assessed in rabbits with long-term indwelling catheters in the epidural space. Motor blockades produced by procaine (1%, 2%, and 4%), lidocaine (1%, 2%, and 4%), and tetracaine (0.5%, 1%, and 2%) in normal saline solution were compared with the effects produced by equimolar amounts of the drug solutions in iophendylate. Procaine (4%) in aqueous solution produced motor blockade lasting 30 ± 3.54 min (mean ± SD) versus 84 ± 4.18 min in lipid solution. Lidocaine (2% and 4%) in aqueous solution produced motor blockade lasting 41 ± 4.18 and 65 ± 6.12 min versus 39 ± 4.18 and 118 ± 10.1 min, respectively, in lipid solution. Aqueous tetracaine (0.5%, 1%, and 2%) produced motor blockade of 106 ± 9.62, 189 ± 6.52, and 273 ± 26.8 min versus 284 ± 14.7, 335 ± 15.8, and 365 ± 26.9 min, respectively, in their lipid counterparts. A control group of animals that received normal saline solution or iophendylate alone did not exhibit motor blockade. These results may be attributed to sustained release of local anesthetics from the lipid vehicle. Hence, lipid drug carriers may be effective in prolonging epidural anesthesia.

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Epidural administration of local anesthetic is considered a relatively safe and reliable method for providing anesthesia, postoperative analgesia, and treatment of chronic pain. Local anesthetic may be administered as a single injection, continuously, or in repeated doses. The action of the drug administered as a single injection is time limited, restricted to procedures lasting <2–3 h. Continuous or repeated administration of the drug requires catheterization of the epidural space. A remarkable increase in the popularity of epidural anesthesia during the past two decades was accompanied by reports of complications related to continuous catheterization. These complications included accidental catheterization of the epidural veins (1–3), migration of the catheter subdurally (4–7) or into the paravertebral space (8,9), knotting (10), and breaking (11) during withdrawal. Prolongation of anesthetic action of a single dose may help to avoid epidural catheterization in some cases, thereby preventing the associated complications. The combination of local anesthetics with a vasoconstrictor has been proposed for such prolongation of epidural anesthesia. Epinephrine was found effective in prolonging the anesthetic action of lidocaine (12–14). However, it was found less effective in combination with long-acting local anesthetics, such as bupivacaine (15,16) or etidocaine (14,17). With the implementation of slow-release systems by the pharmaceutical industry, there were few attempts to introduce them for the prolongation of epidural anesthesia. Slow-release pharmacokinetic profiles (18) and prolongation of nerve blocking effect (19) in dogs, using local anesthetics in liposomal formulations, were reported. In previous studies in rabbits, we showed that the pharmacologic effect was prolonged by intrathecally injecting a lipid solution of 1% tetracaine (20) and 5% meperidine (21). On the basis of this approach, the current study was designed to evaluate the effectiveness of different concentrations of procaine, lidocaine, and tetracaine in prolonging epidural anesthesia using drug preparations incorporated in a lipid vehicle.

Methods

The following experiments were performed in accordance with established laws and guidelines and approved by the Institutional Committee of Laboratory Animal Care. Adult male rabbits of Dutch Belt strain

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(Millbrook Farms, Amherst, Mass.) weighing 2–2.5 kg were used in this study. The animals were housed individually in standard cages, given free access to food and tap water, and kept on a 12-h light/dark cycle.

Long-term catheterization of the epidural space in rabbits was performed using a modification of the procedure previously used for cannulation of the spinal space that we described elsewhere (22). Briefly, operations were performed under aseptic and antiseptic conditions. Polyethylene tubing PE-10 (Clay Adams, Parsippany, N.J.) 300 mm long, 0.61 mm outer diameter, 0.28 mm inner diameter, was used for catheterization. A ring from the tip of a Luer-type plastic syringe, cut 3 mm from the end, was sealed around the catheter 20 mm from the tip. A nylon monofilament suture 6-0 was tied around the catheter 30 mm from the proximal end and fixed with epoxy glue. Disinfection of the catheters was provided by 70% alcohol. Before implantation, catheters were irrigated with distilled water and proximal tips closed with stainless steel plugs. Animals were premedicated with droperidol (1 mg/kg), atropine (0.1 mg/kg), and ketamine (50 mg/kg) subcutaneously. The surgical fields in the dorsal cervical and lumbar areas were shaved and cleaned with iodine/alcohol solution, and 2% lidocaine (3 mL) was injected subcutaneously over the seventh lumbar spinal process. The skin and fasciae were opened between the sixth lumbar and first sacral processes by midline incision, and muscles were separated by blunt dissection. The seventh spinal process was removed and the ligamentum flavum exposed. The slit in the ligamentum flavum was made, and the distal end of the catheter was inserted caudad. The external portion of the catheter was passed subcutaneously, exteriorized via an incision at the dorsal neck, and tied to a buttonlike polyethylene disk implanted subcutaneously. The internal portion of the catheter was fixed to the periosteum of the posterior lamina. Postoperatively, animals were allowed a recovery period of 24 h and then examined.

Three local anesthetics—tetracaine, lidocaine, and procaine—were purchased from Sigma (St. Louis, Mo.) in hydrochloride and free-base forms. Iophendylate (Pantopaque) was purchased from Alcon Laboratories (Humacaol, Puerto Rico) and normal saline solution from Travenol (Baxter Laboratories, Toronto, Canada). All drug solutions were prepared on the day of experiment, and no preservatives were used. Drugs were administered using 0.25-mL Hamilton syringes (Reno, Nev.) and 30-gauge needles using the infusion pump (Harvard Apparatus, South Natick, Mass.). The injection rate was adjusted to 0.25 mL/min. Solutions were injected in volumes of 100 μL/kg. The dead space of the catheter was irrigated by 40 μL of 0.9% sodium hydrochloride. The dead space of the catheters was evaluated previously and found to range from 15 to 18 μL. Equimolar solutions of hydrochloride and free-base drug forms were adjusted on a molecular weight basis.

Because it was not possible to evaluate sensory blockade accurately in the current model, the anesthetic action was assessed by estimating the intensity and duration of motor blockade. This method was used previously in animal models (23–25) and in humans (26,27) as well. Assessment of the local anesthetic action was performed by observing animal movements using criteria suggested by Feldman and Covino (24) for dogs. Motor blockade was graded according to the scale proposed by Bromage (26) for humans, which we modified for the rabbit model as follows: 0 = free movement of hindlimbs without limitation; 1 = limited or asymmetric movement of the hindlimbs to support the body and walk; 2 = inability to support the back of the body on hindlimbs, with detectable ability to move the limbs and respond to pain stimulus; and 3 = total paralysis of the hindlimbs. To evaluate motor blockade, the animals were removed from the restraining hammocks and placed on the floor at 10-min intervals. The intensity of the motor blockade over time was assessed according to the scale just described and displayed on a graph, as proposed by Van Zundert et al. (27).

In a pilot study, we obtained a reproducible motor blockade produced by repeated epidural injections of local anesthetics 24, 48, and 72 h after the operation. We also found that 4–5 days after cannulation, the effect may be reduced owing to the formation of adhesions around the catheter tip. Because each animal served as its own control, our experiments were conducted within the first 72 h after the operation. A separate group of animals was treated by epidural injection of normal saline solution and then by iophendylate to assess the possible influence of the vehicle or the injection procedure on motor blockade.

Postoperatively, animals were randomly assigned to 10 equal groups (five animals in each group). Randomization was performed before anesthetic administration using a blind combination of two groups of cards. Set 1 contained one card for each rabbit, each of which was assigned a number. Set 2 included nine groups labeled with the name of the drug (lidocaine, procaine, or tetracaine) and a code (A, B, or C) and one group labeled normal saline solution. For the selection of dosage, an "up-and-down" adjustment method was used. If a third-degree block was produced by the initial dose, the next administered dose was decreased twofold. If the initial dose produced only a first- or second-degree block, the subsequent injected dose was doubled. The duration and intensity of the motor block were assessed. Twenty-four hours after injection of the aqueous solution, an equivalent amount of the drug in lipid solution was administered, and motor blockade was again evaluated. The investigator who evaluated the motor blockade was unaware of the identity of the injected solutions. The order of injections (aqueous solutions before lipid solutions) was used because iophendylate remains in the epidural space for a long time. The presence of lipid substance close to the site of injection affects redistribution of the injected drug. Therefore, animals that receive lipid solutions cannot be used for additional experiments.

Concentrations that produced effect in both drug forms were selected for comparison. Finally, three concentrations of each drug were assessed.

Duration, maximal intensity, and onset period of maximal blockade were analyzed by nonparametric tests (Mann-Whitney or the Kruskal-Wallis test, followed by nonparametric Tukey-type multiple-comparisons tests, when appropriate). Differences among variables obtained from lipid versus aqueous solutions within the same animal group were analyzed using the Friedman test. A P value <0.05 was considered the limit for significance.

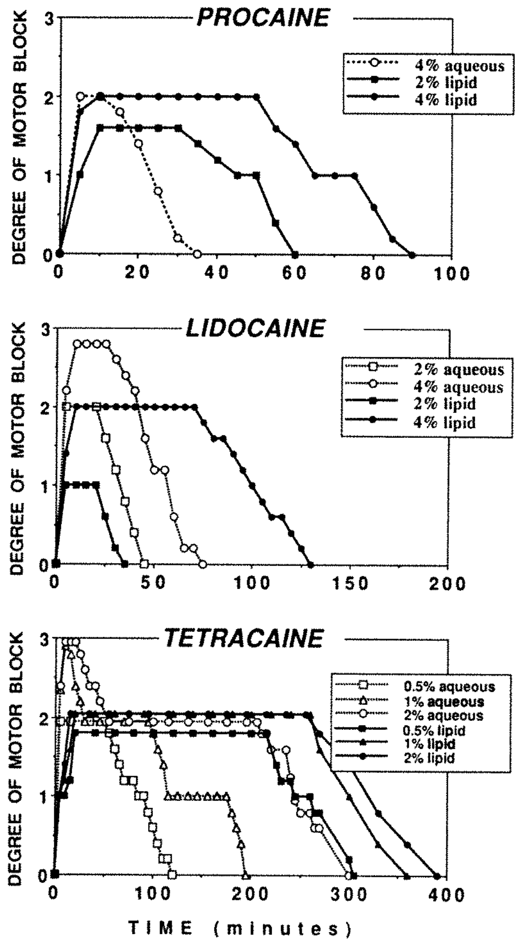

Figure 1. Time-course of motor blockade in response to epidural injections of lipid (iophendylate) versus aqueous (normal saline) solutions of procaine, lidocaine, and tetracaine.

Results

All animals awoke and moved actively using all four limbs within 1 h after the operation. None of the animals developed neurologic deficit or inflammation in the area of the surgery postoperatively. The injections of drugs in the doses assessed during the experiments were easily tolerated by all animals and did not cause noticeable discomfort. However, animals became agitated at attempts to inject the anesthetics in concentrations >4%. Pain was probably caused by the high osmolarity of the administered solutions. The maximal concentration of the injectate was therefore limited to 4%. Finally, the following solutions were assessed: 1%, 2%, and 4% of procaine; 1%, 2%, and 4% of lidocaine; and 0.5%, 1%, and 2% of tetracaine. The duration and intensity of the motor blockade produced by epidural injection of the drugs are expressed graphically in Figure 1.

Administration of 2% procaine in normal saline solution and 1% procaine or lidocaine in both (lipid or aqueous) solvents did not produce motor blockade in any of the treated animals.

The intensity of motor blockade produced by epidurally injected local anesthetics in the same solvent increased as a function of drug dosage. A significant increase in the intensity of the motor blockade, as a result of increasing the drug concentration, was found among lipid solutions of 2% and 4% lidocaine, aqueous solutions of 2% and 4% lidocaine, and aqueous solutions of 0.5% and 1% or 2% tetracaine. Differences among the maximal effects produced by other solutions did not reach significant levels.

The onset of maximal motor blockade produced by aqueous and lipid solutions of the drugs ranged from 5 to 10 and 5 to 20 min after the injection, respectively. No significant differences were found between these onset periods among different concentrations of drugs in the same preparation form. Duration of motor blockade significantly increased with the increase of the injected dose among all of the anesthetics tested (Figure 1).

A comparison between the effects produced by equal concentrations of anesthetics in aqueous versus lipid solution revealed the following results: (a) aqueous and lipid solutions of 4% procaine produced a similar intensity of motor blockade; (b) aqueous solution of 2% procaine did not produce motor blockade in contrast to the lipid preparation, which produced motor blockade in all treated animals; and (c) aqueous solutions of lidocaine and tetracaine produced significantly higher degrees of motor blockade than equivalent concentrations of lipid preparations, except for 0.5% tetracaine, which produced similar degrees of motor blockade in both preparations.

Motor blockade produced by aqueous and lipid solutions of procaine and lidocaine reached maximal effect between 5 and 10 min and did not show significant differences between the two preparation forms. Motor blockade produced by aqueous and lipid solutions of tetracaine reached maximal values within 5–10 and 10–20 min, respectively. The differences between the two formulations were significant in all three concentrations tested. A comparison between the durations of motor blockade produced by equivalent drug concentrations in different solvents showed a significant prolongation of motor blockade in animals treated by lipid solutions, except for 2% lidocaine (Figure 2). Durations of motor blockade produced by assessed solutions and ratios between equivalent anesthetic concentrations in the lipid versus aqueous preparation are presented in Figure 2.

Animals treated by epidural administration of normal saline solution or iophendylate did not show any degree of motor blockade.

Discussion

Our study examined the possibility of prolonging epidural anesthesia by using a lipid drug carrier. The mechanism for prolonging the local anesthetic action in this study was based on the different solubilities of two drug forms (salt and free base) in aqueous and lipid solvents. The water-soluble salt form of the drug was dissolved in normal saline solution. The lipid-soluble free-base form of the drug was dissolved in iophendylate, which was synthesized as iodized fatty acids. (The base form of most local anesthetics is lipid soluble and nearly insoluble in water [28].) Clinical use of iophendylate in humans is controversial because of the possibility of aseptic arachnoiditis. We used iophendylate in our study as a model of a lipid drug carrier. Other lipids or lipid-based vehicles (e.g., liposomes, emulsions) may be suggested and developed in the future. In each case, pharmacologic and toxicologic studies will be required before final implementation of any new formulation in clinical practice.

Local anesthetics injected into the epidural space in aqueous solutions easily diffuse into the interstitial fluid and are then absorbed by epidural fat and neural roots. Local anesthetics injected epidurally in lipid solution to reach the neuraxis need to diffuse from the lipid medium into the interstitial fluid. The base form of the anesthetics is insoluble in aqueous medium and therefore should pass preliminary ionization. Because the process of ionization is limited to the surface between the lipid and aqueous milieu, only a small amount of the drug is available to pass it and diffuse from the solvent toward the neuraxis at any given time. Hence, the lipid solvent serves as a drug depot, and the injected solution acts as a sustained-release formulation.

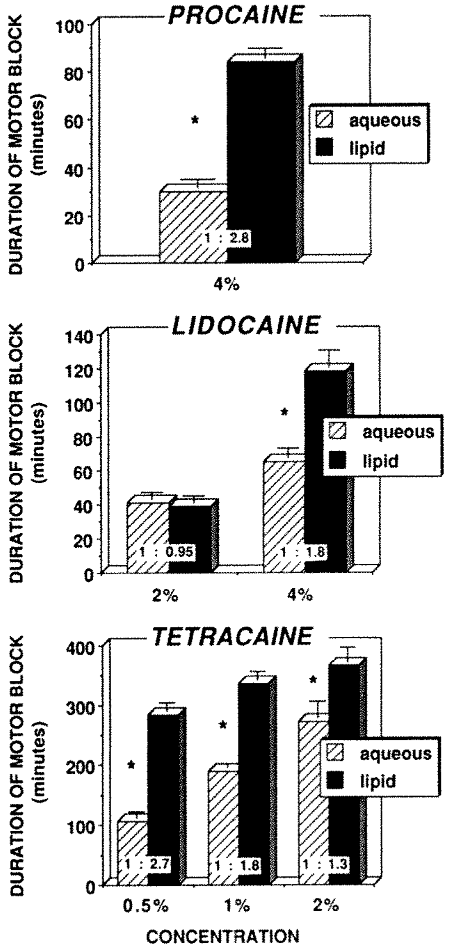

Figure 2. Duration of motor blockade produced by epidural injection of procaine, lidocaine, and tetracaine. *Hatched* and *solid bars*, mean responses to injections produced by equivalent concentrations of anesthetic in aqueous versus lipid solution, respectively; *numbers in boxes*, aqueous/lipid ratio of duration; *error bars*, SEM. *Significant differences between durations produced by the aqueous and lipid solutions.

We injected various concentrations of procaine, lidocaine, and tetracaine epidurally in aqueous and lipid solutions and assessed their anesthetic action by evaluating the intensity and duration of the motor blockade. We believe that it would have been preferable to use sensory in addition to motor blockade to evaluate anesthetic action in the present study, but for technical reasons, the current model did not permit us to evaluate sensory blockade for longer than 2 h. We acknowledge that some discrepancy may exist between motor and sensory blockade. However, the pattern of their action is similar, and their molecular mechanism is the same. Therefore, motor blockade has previously been used as a marker of local anesthetic action (23–27), and we used it to compare the effects produced by aqueous and lipid solutions of local anesthetics in the current study.

A comparison between the effects produced by two different treatments can be designed in two distinct ways: using two different groups of patients or using each patient as his or her own control. The latter design is optimal if the order of treatment is randomized. In our study, a constant order of injections (aqueous solutions always before lipid solutions) did not permit randomization of the aqueous and lipid injections. However, we believe that by randomizing the injections of the aqueous solutions, using different investigators to inject the drug and to evaluate the effect, and not informing the latter investigator of the identity of the injected solution, we avoided the influence of bias on the results.

Our study showed that epidural injection of local anesthetics in lipid solutions produced a longer effect than the injection of aqueous drug solutions. This prolongation of anesthetic action may be attributed to the limited rate of drug release from the lipid solvent. Our data suggest that a lipid drug carrier can be used as a vehicle in a slow-delivery system for prolongation of local anesthetic action.

A comparison between the effects produced by two formulations of 2% lidocaine, which was the lowest effective concentration in the present study, showed a decrease of the motor blockade duration produced by the lipid preparation. This might occur because the relatively small amount of anesthetic released from the lipid solution was insufficient for maintaining the drug concentration on the nerve tissue at an effective level. Evidently, when the concentration of the lidocaine was increased to 4%, the lipid solution of the anesthetic produced a significantly longer motor blockade than the aqueous solution.

Lipid solution of 2% procaine produced motor blockade of second degree in all treated animals, but an equivalent amount of the drug in aqueous solution did not produce any effect. Most likely, because of the poor lipid solubility of procaine (29), its uptake from the aqueous solution into nerve membranes or epidural fat is relatively low. Therefore it is possible that a considerable portion of the drug undergoes vascular absorption by bulk flow before reaching the neuraxis. Lipid solution of procaine was absorbed very slowly and remained in the epidural space for a longer period of time. Evidently, the rate of the procaine release from the lipid solution was sufficient to maintain an effective concentration on the nerve tissue. As a result, lipid solution of 2% procaine produced motor blockade, and the equivalent concentration of aqueous solution did not produce any effect.

Finally, among local anesthetics tested in this study, only tetracaine was effective in producing considerably prolonged motor blockade. This is most likely due to its exclusively slow release from the iophendylate. This may be explained by the strong affinity of tetracaine to a lipid vehicle (30) owing to its high partition coefficient (29), compared with those of lidocaine or procaine. The duration of effect produced by different concentrations of lipid formulations of tetracaine lasted from 5 to 7 h. This finding clearly indicates that appropriate lipid formulations of local anesthetics may considerably prolong epidural anesthesia. Hence, the development of lipid or lipid-containing vehicles for local anesthetics may, in particular cases, be helpful in avoiding the continuous catheterization of the epidural space and in replacing it with single injection of drug.

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Subblocking Concentrations of Local Anesthetics: Effects on Impulse Generation and Conduction in Single Myelinated Sciatic Nerve Axons in Frog

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Phenomena seen in axons exposed to subblocking doses serve as the basis for interpreting clinical and behavioral observations during onset and recovery of peripheral nerve block. To delineate the changes in excitability and in impulse conduction caused by subblocking concentrations of local anesthetics (LAs) in myelinated peripheral nerve fibers, LAs were applied to excised frog sciatic nerves while impulse conduction was monitored in single axons. For concentrations ranging from 0.01 to 1.2 times the LA concentration needed to block impulse conduction, three measures of susceptibility to LA were made to quantify the action of the drugs on "resting" fibers (firing rates ≤0.5 Hz): the increase in the threshold for electrical activation of impulses, the increase in conduction latency reflecting the slowing of impulse conduction in the region exposed to LA, and the "critical blocking concentration" of LA just sufficient to prevent impulse conduction in the recorded fiber. Wide interfiber variation in these variables was observed (e.g., for lidocaine, latency increases at block ranged from 66% to 257% of control, blocking concentrations ranged from 0.29 to 1.40 mM), which was not correlated with fiber diameter (as indicated by resting conduction velocity). Mathematical modeling of impulse conduction in fibers exposed to LA demonstrated that the interfiber variation in susceptibility to LA block could result from interfiber differences in the density of sodium and potassium channels. The effects of LA were also studied in active fibers (firing rates >0.5 Hz). Local anesthetics reversibly inhibited two normally occurring afteroscillations in membrane threshold related to afterpotentials following an impulse. These were "superexcitability," a transient lowering of threshold lasting as long as 1 s, and "depression," a phase of raised threshold peaking within 2–4 s after an impulse and recovering slowly over several minutes. Impulse activity also transiently increased the apparent potency of LAs. Such "use-dependent" increases in threshold and decreases in conduction velocity showed kinetics that were agent specific, lasting 1 s after a burst of impulses for lidocaine and lasting >10 s for bupivacaine. At low concentrations, within the range of nontoxic plasma concentrations after systemic administration, the predominant actions of LAs on conducting fibers were transient decreases in excitability and conduction velocity in combination with a reduction of intrinsic oscillatory aftereffects of impulse discharge. These effects may degrade decoding of information in discharge patterns without actually blocking conduction of infrequent impulses, suggesting how functional blockade of coordinated movement and perception may occur even without complete blockade of impulse conduction.

(Anesth Analg 1992;75:906–21)

During onset and regression of peripheral nerve blocks with local anesthetics (LAs), the nerve fibers are exposed to subblocking concentrations. Psychophysical studies of partially blocked nerves have shown a curious failure of function even under conditions where blockade of impulse conduction is incomplete, as in the case where the sensation of cooling the skin is prevented even though Aδ fibers can still conduct impulses in response to electrical stimulation (1). The intent of the experimental studies reported here has been to observe and describe the actions of LAs on the processes underlying impulse conduction. These processes also modulate membrane excitability and thereby influence impulse generation in fibers. By studying excitability and latency in conducting fibers subjected to patterns of impulse discharge ranging from isolated impulses to high-frequency trains, we hoped to derive an integrated picture of the interactions between LAs and impulse activity.

The basis for the anesthesia produced by LAs was first deduced from observations of compound action potentials, which decreased in amplitude as the im-

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pulses in individual fibers were blocked. It is now established that the primary mechanism of this blocking action is the attenuation of depolarizing Na^+ current as documented by voltage-clamp studies of squid axon and of single nodes of Ranvier, and more recently by studies of small patches of membrane containing one or more ion channels (2). The effects of LA on propagated impulses in individually recorded conducting fibers were first reported by Franz and Perry (3). That study and subsequent work with single fibers of vagus nerve (4) provided important evidence *against* the size principle of susceptibility to LA, which has held that susceptibility of axons to conduction block by LA depends on axon diameter, being greater for smaller diameter axons (5). Given the doubt about the relevance of axon size determining differential susceptibility, it is important to learn what other factors may be important. Our work was done to characterize how sensitive particular axons are to LA and to investigate the extent and basis for interfiber variation.

We have studied actions of LAs on individually recorded myelinated fibers in a mixed nerve where 2–6 cm of the conduction path was exposed to LA, exceeding the exposure length over which decremental conduction will substantially raise the concentration of LA (abbreviated here as [LA]) needed to block impulse propagation (6). By tracking both the speed of impulse propagation (by measuring the conduction latency) and the level of stimulation needed to generate an impulse (by measuring the firing threshold), it is possible to observe effects of LAs at subblocking concentrations for impulse conduction. Because action potentials thus continue to conduct, it was also possible to study the interactive effects of impulse activity and LA, some of which are revealed in the intact fiber but have not been reported in studies of dissected nodes or isolated channels. These include afterpotentials and afteroscillations in membrane excitability, which are intrinsic to conducting fibers (7) and which may be important in impulse interval coding (8–10). Disruption of such codes may block the "message" of the fiber without preventing conduction of all of the impulses carrying the message (11).

Methods

Sciatic nerves were excised from large frogs, *Rana pipiens*, after pithing of brain and spinal cord by experienced personnel. The investigations were authorized in proposals approved by the Harvard Medical Area Standing Committee on Animals. This report is based on integrated observations from 170 nerves and >200 fibers.

Nerve Support

The nerves were placed in a Boyle-Conway saline-glucose solution bubbled with 3%–6% CO_2 in air, containing (in mM): NaCl 80.5, KCl 2.1, $CaCl_2$ 1.8, $MgSO_4$ 1.2, Na_2SO_4 0.66, $NaHCO_3$ 25.0, Na_2HPO_4 2.6, KH_2PO_4 0.5, and glucose 3.3. The Pco_2 was adjusted to hold pH at a constant value (±0.05 pH units) between 7.3 and 7.4. Temperature was regulated at 18 ± 0.5°C using a Peltier device. The nerve sheath was left intact except for the last 1 cm of the conduction path, where fibers were teased apart for recording with small-diameter plastic suction electrodes. Two pairs of stimulating electrodes were used, one to condition the fiber by evoking trains of conducted impulses and the other to test for threshold by applying stimuli just strong enough to activate the single fiber under study. Stimulating pulses were monophasic current pulses the intensity and duration of which were adjusted either to be well above threshold for conditioning or to be at threshold for testing the membrane excitability. Fibers could be studied for ≥2 days under these conditions, so most data are from one fiber per nerve.

Excitability Measurement and Determination of Blocking Concentration

Impulse conduction velocity (conduction distance divided by the latency) and the threshold for electrical activation of a conducted impulse (threshold [in coulombs], the product of pulse current intensity and pulse duration) are indications of the relative excitability of the membrane. Latency was measured for each conducted impulse using a latency meter that we constructed to produce a voltage proportional to the time interval between the rising edge of the stimulus and the arrival of an impulse at the recording electrode. The impulse was detected by a Schmitt trigger set to undergo a transition during the steepest section of the rising phase of the impulse, thus minimizing the temporal fluctuations resulting from recording noise. Threshold was "hunted" (7) by adjusting the stimulus strength automatically so as to maintain the probability of triggering a conducted action potential at 50%. This was achieved by a decremental decrease of the stimulus after a response and an incremental increase by the same small amount (0.25%–1% of either the duration or the amplitude of the stimulus pulse) after each failed stimulus. Local anesthetics (lidocaine, bupivacaine, and 2-chloroprocaine) supplied by ASTRA Pharmaceuticals (Westborough, Mass.) were dissolved in Boyle-Conway solution at concentrations such that adding 0.1 mL to the solution bathing the conduction path would raise the bath concentration of LA by

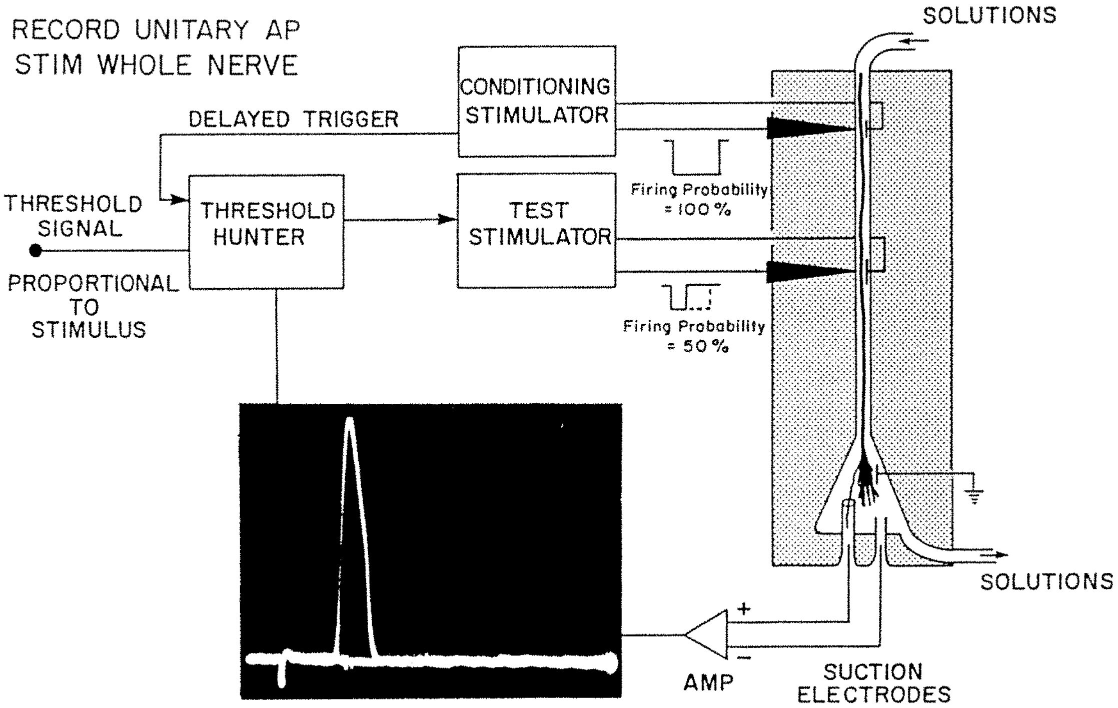

Figure 1. Diagram of preparation. The action potential (AP) *inset* is a photograph from the oscilloscope showing two overlapping sweeps. One was a flat trace after a failed stimulus at slightly below threshold intensity, and the other exhibited a unit potential recorded from a large fiber at the far end of the conduction path after a successful stimulus just above threshold intensity. Thus, traces were either flat (note the baseline under the potential) or unitary with an easily detected spike, and the entire conduction path including the recording site could be exposed to local anesthetic in the circulating solutions without obscuring the detection of impulses. The threshold hunter controlled both the amplitude and duration of stimuli. It lowered the next stimulus whenever an action potential occurred and raised it whenever the stimulus failed, thus converging on the 50% firing probability. Latency was measured for conduction from the test electrode (connected to the "test stimulator") to the tip of the recording electrode (5–6 cm).

0.1 mM (Figure 1). To measure the blocking concentration of LA, [LA] was increased in steps, each followed by an equilibration time. The critical blocking concentration (C_b) was determined by interpolation between the highest nonblocking dose and the next increment in [LA] that resulted in conduction failure during the equilibration time. The interpolation was based on exponentials fit to the latency increases measured in the fiber before blockade (Figure 2B). In all cases of blockade, the impulses were restored on washing with LA-free solution. For fiber 25 (Table 1) the C_b was replicated three times by repeated 0.05-mM supplements and dilutions at 1.35-mM concentration.

Tonic and Phasic Effects

A "tonic" action of LAs on excitability was determined by using infrequent test stimuli given at sufficiently long intervals (2 s for lidocaine and 2-chloroprocaine; 20 s for bupivacaine) that any "phasic" or transient effects of previous impulses had decayed. Conditioning impulses given at such long intervals are called "singlet" conditioning pulses (CPs). Effects of impulse activity in the presence of LAs were studied by stimulating the nerve with conditioning bursts of 1–64 CPs and then testing the threshold at various delays afterward. The transient afteroscillation in threshold was plotted by incrementing the delay of the test stimulus from the singlet CPs or from the last pulse of repeated conditioning bursts. The rate of repetition was determined empirically to be slow enough that no cumulative effect on tonic threshold was seen.

Means are reported ± the SD based on the number of degrees of freedom ($N - 1$). Correlation coefficients (r) were calculated by linear regression under Quattro Pro 3.0 (Borland, Scotts Valley, Calif.); Z scores were computed by multiplying r by the square root of the number of degrees of freedom, and r values were considered significant for $P < 0.01$.

Mathematical Models

Computer simulations of conducted action potentials were used to determine the degree of interfiber variation in susceptibility to LAs that would be expected on the basis of variations in densities of

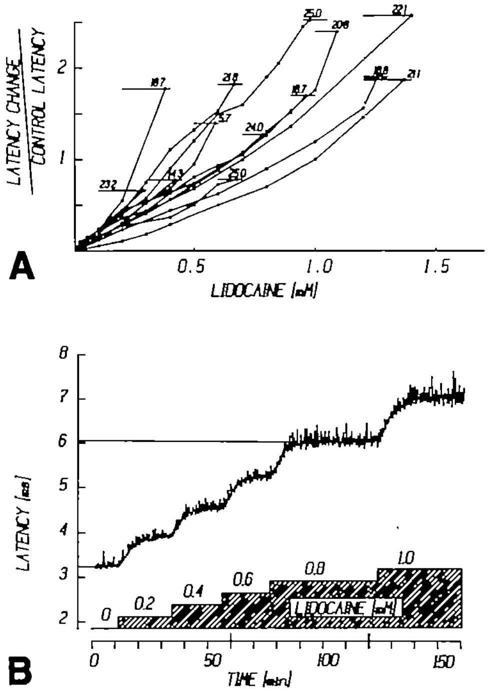

Figure 2. A. The fractional increase in latency (the increase in latency normalized by the resting latency) was measured (*circles*) after equilibration to increments of lidocaine concentration. The resting conduction velocity (m/s) for a particular fiber before application of lidocaine is shown above the *horizontal line* terminating each curve, which is drawn at the maximal latency attained before conduction block. The line spans the increment in lidocaine concentration between the last concentration at which equilibration was complete without block and the next increment in concentration that resulted in block at or before complete equilibration. Latency for each conducted impulse was plotted throughout the exposures (as shown in part B for example, Fiber 4 in Table 1; stimuli at 0.5 Hz). The steady-state latency reached after each increment was taken graphically by fitting a line by eye to the lower edge of the commonly occurring latencies (for example, the bottom of the "*solid*" part of the trace, as shown for the control latency and the latency after equilibration with 0.8 mM lidocaine). The occasionally longer latencies, appearing as spikes in the temporally compressed curve, occur because of delays in the generation of conducting impulses that can result when stimulation is near the threshold (9). During the equilibration to the highest concentration, the latency-versus-time plots were used to estimate whether equilibration had just begun or was nearly complete before the block in impulses occurred, and thus to interpolate a value for the critical blocking concentration (C_b). Slope sensitivities were measured at half the C_b.

voltage-gated ion channels. The mathematical model for the squid giant axon of Hodgkin and Huxley (12) was modified for myelinated frog fibers as follows. The ionic currents at nodes (i_{HH}) were given by Crank-Nicholson integration (13) of Equation (1) at 25-μs intervals for each of 31 sequential nodes connected by passive internodes:

$$i_{HH} = \bar{g}_{Na}m^3h(v - E_{Na}) + \bar{g}_K n^4(v - E_K) + g_l(v - E_l), \qquad (1)$$

where $\bar{g}_{Na}$ and $\bar{g}_K$ are the maximal specific conductances for Na^+ and K^+ and g_l is the voltage-independent "leak" conductance; E_{Na}, E_K, and E_l are the Nernst equilibrium potentials for Na^+, K^+, and leak-permeable ions; and m, h, and n range between 0 and 1, depending on membrane voltage and time according to equations of the type

$$dm/dt = \alpha_m - (\alpha_m + \beta_m)m, \qquad (2)$$

and similarly for dh/dt and dn/dt, where α and β are rate constants that depend only on membrane voltage and temperature and at 18.5°C, the temperature of the simulation, are given by

$$\alpha_m = 3.82[0.1(-V + 25)/e^{(-V+10)/10} - 1],$$

$$\beta_m = 3.82[4e^{-V/18}], \qquad (3)$$

$$\alpha_h = 3.82[0.07e^{-V/20}],$$

$$\beta_h = 3.82[1/(e^{(-V+30)/10}+1)], \qquad (4)$$

$$\alpha_n = 3.82[0.01(-V + 10)/(e^{(-V+10)/10} - 1)],$$

$$\beta_n = 3.82[0.125e^{-V/80}], \qquad (5)$$

where V is the membrane potential relative to a resting potential of -65 mV, and v in Equation (1) is the now conventional membrane potential inside relative to outside (i.e., v = -65 mV, when V = 0 mV). Values adopted for the fixed parameters were $\bar{g}_{Na}$ = 1.20 mho/cm^2 at nodes and 0.0 mho/cm^2 at internodes; $\bar{g}_K$ = 0.36 mho/cm^2 at nodes and 0.0 mho/cm^2 at internodes; g_l = 0.001 mho/cm^2 and capacitance = 1 μF/cm^2 for nodal, internodal, and Schwann cell membrane; E_{Na} = +50 mV, E_K = -77 mV, and E_l = 54.402 mV. The passive internodes were each represented by five separately computed segments of 10-μm diameter wrapped with 250 layers of myelin, which was modeled as decreasing the leakage conductance and the membrane capacitance in proportion to the reciprocal of the number of myelin layers (1/250).

Tonic blockade of Na^+ channels was modeled as a first-order process by reducing the density of available channels, $\bar{g}_{Na}$, by the factor $K_d/([LA] + K_d)$, where K_d is the equilibrium dissociation constant (in mM) for binding of LA to Na^+ channels, and [LA] is the concentration of LA (in mM). The tonic blockade of K^+ channels was also incorporated into this model by multiplying $\bar{g}_K$ by the analogous factor for binding of LA to K^+ channels. Use-dependent binding is an incremental effect mainly on Na^+ channels that occurs during the depolarization for each action potential. Use-dependent binding was modeled by multiplying a proportional rate constant for forward binding (0.5 ms^{-1}·mM^{-1}) by the [LA], by dt, and by the fractional increase in Na^+ conductance during the action potential, $g_{Na}(t)/\bar{g}_{Na}$, (14), where the depolarization exceeded 3% of the resting potential. The unbinding of LA from these phasically bound chan-

Table 1. Tonic Susceptibility Measures for Lidocaine

Fiber No.[a]	Resting CV[b]	Slope sensitivity[c] (% change/mM)	C_b[d] (mM)	Change in threshold[e]	Change in latency[e]	Fiber No.[a]	Resting CV[b]	C_b[d] (mM)
1	21.8	304.6	0.66	3.9	1.82			
2	21.1	99.8	1.39	1.8	1.87	14	18.7	0.50
3	18.7	414.0	0.38	4.3	1.77	15	13.3	1.00
4	18.8	123.0	1.26	3.2	1.91	16	8.0	1.30
5	25.0	108.2	0.68	1.8	0.78	17	14.0	0.60
6	25.0	262.0	0.98	5.0	2.53	18	21.0	0.60
7	20.8	164.1	1.09	5.5	2.40	19	20.6	1.25
8	5.7	192.5	0.59	2.7	1.39	20	22.6	0.90
9	24.0	137.5	0.78	1.5	1.27	21	7.7	0.90
10	18.7	160.2	0.96	3.6	1.70	22	17.7	1.00
11	14.3	177.4	0.42	1.5	0.78	23	5.7	0.40
12	23.2	232.0	0.29	3.0	0.66	24	19.2	1.30
13	22.1	169.3	1.40	4.8	2.57	25	28.8	1.36

[a] Fibers 1–13 and 25 were exposed to lidocaine over the entire conduction path. Thresholds and latencies were measured throughout the exposure and wash. In fibers 14–24, the critical blocking concentrations (C_b) were measured with 2–3 cm of the conduction path exposed to lidocaine, and thresholds were not measured. Mean (± SD) C_b = 0.88 ± 0.35 mM.

[b] There was no significant correlation of the resting conduction velocity (CV) with measures related to conduction safety (i.e., with C_b, maximal change in threshold, or maximal change in latency).

[c] Slope sensitivity, expressed as percent change in latency per mM, did not predict the degree of maximal increase in latency ($r = 0.134$) but was weakly indicative of the blocking concentration ($r = 0.51$; $P < 0.045$ for latency slope sensitivity vs C_b).

[d] Fibers most resistant to block tended also to show the largest maximal latency ($r = 0.72$; $P < 0.009$ for maximal latency and C_b).

[e] Fibers showing a large increase in latency also showed a large increase in threshold ($r = 0.78$; $P < 0.005$ for maximal latency vs maximal threshold).

nels was modeled by multiplying a reverse proportional rate constant, 0.025 ms^{-1}, (14) by the proportion of phasically bound channels and by dt. I wrote the model as a FOCAL program in the CABLE environment (13) supplied by Dr. Michael Hines, and the simulation was run on an Everex Step 20 80386 microcomputer. Percentage changes in latencies for conduction of action potentials from the first to the 25th node in the model were exported to Generic Cadd (Generic Software, Bothell, Wash.) and plotted on an HP Laserjet III offset printer.

Results

Tonic Actions on Excitability and Blockade

Stepwise increases in [LA] result in progressive increases in the firing threshold (15) and in the latency of impulse conduction (Figure 2). After each step in [LA], the latency and threshold initially increased rapidly, arriving at a new stable level over the course of 7–25 min (sheath intact), reflecting equilibration of the LA with sites distributed along the axon in the exposed region of the nerve. The latency at steady state was longer at higher concentrations, and impulses were conducted at their slowest possible rate in these fibers at [LA] values just below those causing conduction failure. The increase in latency before block with lidocaine in the population of 13 A-fibers exposed over the entire conduction path to blocking concentrations ranged from 66% to 257% of the control latency, revealing significant interfiber variation (Figure 2). The tonic blocking concentrations were interpolated (see Methods) using records tracking the latency for each conducted impulse (such as in Figure 2B). Blocking concentration (C_b) is a traditional measure of susceptibility of an axon to LA, and the range of C_b values measured to within 0.05 mM in 25 fibers (0.29–1.40 mM) is a second indication of interfiber variation in susceptibility (Table 1).

Another measure of tonic susceptibility to LA that can be used to compare susceptibility to LA among different fibers at subblocking concentrations is the "slope sensitivity" of a fiber, referring to the degree of slowing (or of raised threshold) per unit increase in [LA]. Exposure to weak concentrations (e.g., <0.3 mM lidocaine in Figure 2A) was sufficient to differentiate axons according to this measure, and axons that showed a high slope sensitivity relative to the other fibers at low concentrations tended to preserve their relative susceptibility by this measure over higher concentrations (Figure 2A). However, high slope sensitivity to LA did not necessarily ensure that block would occur at low concentrations, because in some fibers the latency increase before block could be more than three times greater than in other fibers. The maximal change in threshold before block (Table 1) also was not strongly correlated with C_b ($r = 0.29$), although maximal latency change was larger for axons with higher C_b ($r = 0.72$; data from Table 1). Despite its weak correlation with C_b ($r = 0.51$), the latency slope sensitivity was not a reliable

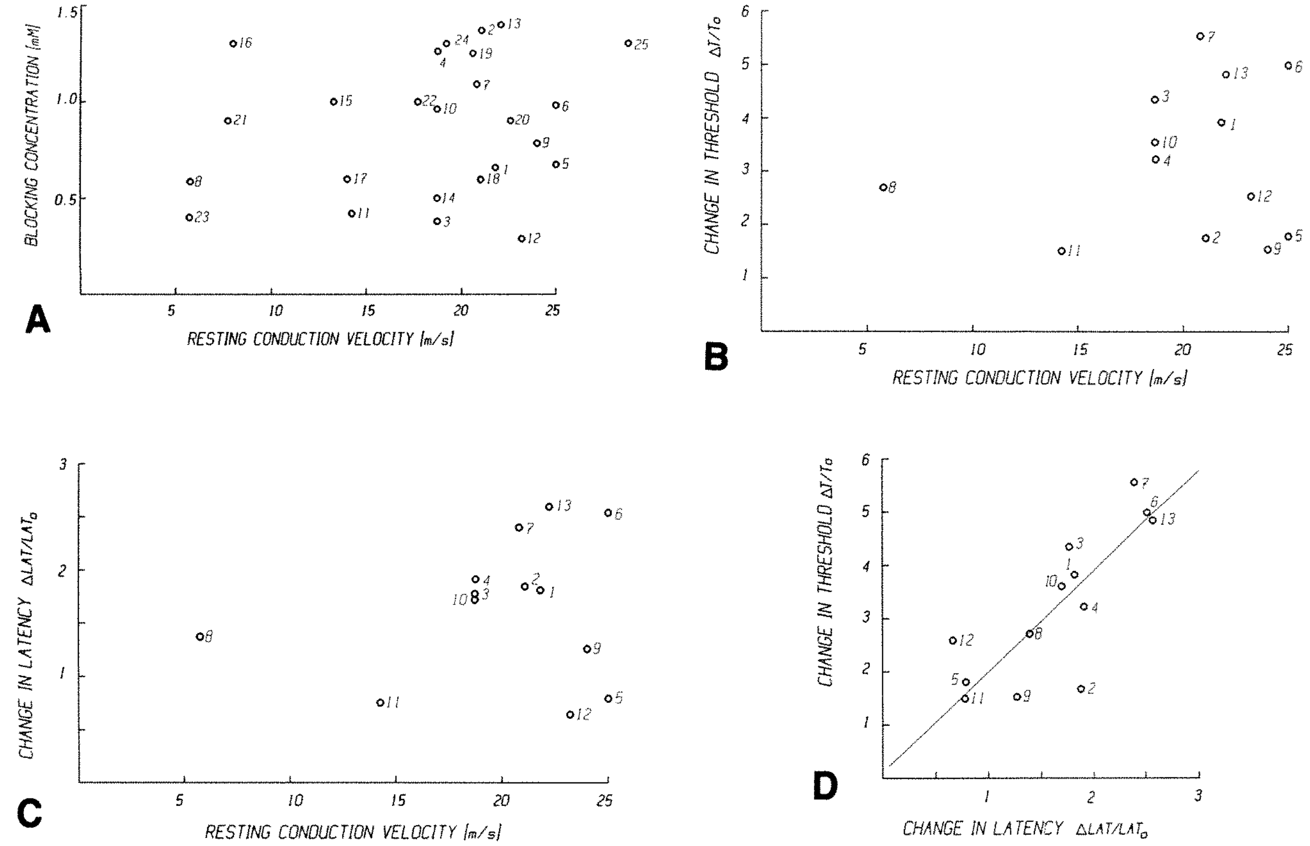

Figure 3. Susceptibility versus conduction velocity (CV). **A.** Tonic blocking local anesthetic concentration [LA] versus resting CV for 25 axons exposed over lengths >2 cm and for which the critical blocking concentration (C_b) is known within 0.1 mM (r = 0.23; $P < 0.15$). **B.** Maximal change in the tonic threshold as a factor of control threshold (difference in the product of stimulus current [mA] times stimulus pulse duration [μs] measured just before block of impulse conduction and that measured under control conditions before application of lidocaine divided by the control threshold) versus CV for 13 fibers (r = 0.17; $P < 0.29$). **C.** Maximal change in latency (ΔLAT) as a factor of the control latency (difference between latency measured just before block and control latency normalized by the control latency) versus CV for the same 13 fibers as in **B** (r = 0.16; $P < 0.29$). The fibers in **A** and **B** were exposed over the entire conduction path. *Data points* from each fiber are from Table 1. **D.** Significant correlation between the maximal change in threshold before block in a given fiber (**B**) and the maximal change in latency (ΔLAT) for the same fiber (**C**) (r = 0.78; $P < 0.005$).

predictor of blocking concentration. For example, the five fibers conducting at 14.3, 24.0, 18.7, 20.8, and 22.1 m/s in Figure 2A show nearly overlapping slope sensitivity for latency (138%–177%/mM determined at $C_b/2$), yet range in C_b from 0.42 to 1.4 mM. These two measures of susceptibility to LA (latency slope sensitivity and C_b) thus varied somewhat independently among fibers, indicating that multiple factors in the axon govern its sensitivity to LA.

None of the measures of blocking susceptibility to LA (C_b, the maximal threshold increase, or the maximal latency increase before block) were strongly related with resting conduction velocity (Figure 3A–C). Axons showing larger increases in threshold after a dose of LA also tended to show relatively larger increases in latency. The maximal changes in latency and threshold shown just before block (Table 1) reflect this correlation (r = 0.78; Figure 3D).

Simulations of Interfiber Variation

Mathematical models of impulses conducting in single frog axons have been used to test whether variation in the density of Na^+ and K^+ channels could account for interfiber variation in tonic susceptibility to LA. Structurally, the model fiber used for the data shown in Figure 4 was 10 μm in axon diameter, with nodes 1.3 mm apart and internodes wrapped by 250 layers of myelin (see Methods). Its resting conduction velocity was 22.8 m/s over a conduction distance of 3.25 cm with no LA present. Changing only the density of K^+ channels ($\bar{g}_K$) over a range of 40%–200% of the control density (Figure 4) changed the resting conduction velocity (CV) by <10% (24.2 m/s for 40% $\bar{g}_K$ and 20.5 m/s for 200% $\bar{g}_K$), but it altered slope sensitivity measured at half the C_b by >65% (72.4% per mM for 40% $\bar{g}_K$, 98.8% per mM for

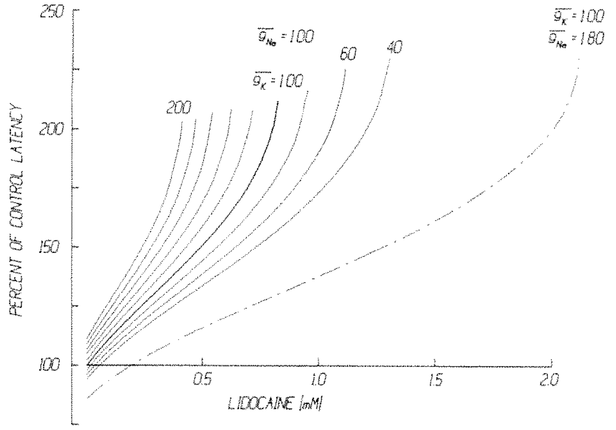

Figure 4. Change in latency during exposure to lidocaine as predicted from a computer model of conducting frog fibers (13,32). A family of curves relates the percentage increase in latency to lidocaine concentration in the same manner as the experimental results shown in Figure 2. Curves were calculated for a 10-μm-diameter fiber with 1.3-mm passive internodes at 18.5°C. Latency was measured for a propagated action potential stimulated at node 0 and recorded 25 nodes away when the membrane potential at that node crossed −30 mV. Block (defined when the membrane potential of the 25th node did not increase above −30 mV) was titrated to within 10 μM. Thus, the last plotted latency was measured for exposure of 25 identical nodes to a lidocaine concentration (K_d for g_{Na} = 0.2 mM; K_d for g_K = 0.6 mM) within 10 μM of that required to block propagation. The nodal density of Na^+ channels was taken as proportional to the Hodgkin and Huxley (12) variable $\bar{g}_{Na}$ (10 times $\bar{g}_{Na}$ for squid giant axon [32]). It was assumed that all 25 nodes were alike in $\bar{g}_{Na}$ and in $\bar{g}_K$ (19). Curves were plotted for 20% increments of the nodal density for K^+ channels over the range 40%–200% of the "normal" value (10 times the $\bar{g}_K$ for squid giant axon). Increasing K^+-channel density increased the slope sensitivity of the model fiber to lidocaine while simultaneously decreasing C_b. Thus, with the model, C_b and slope sensitivity were correlated, whereas experimental results on different fibers showed little correlation, suggesting that additional variables as well as channel densities vary from fiber to fiber. Decreasing and increasing K^+-channel density (Na^+-channel density held constant at 100%) altered resting latency over a range of −7% and +11% of the control condition (*bold curve*, $\bar{g}_K$ and $\bar{g}_{Na}$ = 100%). The *dashed curve* shows the effect of increasing the density of Na^+ channels to 180% of control without changing the K^+-channel density (at 100%). This reduced the slope sensitivity (44.6% per mM at $C_b/2$) with a parallel increase in C_b (to 2.10 mM). The maximal latency increase before block was only slightly greater than for the other ratios of channel densities shown. (See text for explanation of variables).

control, and 167.8% per mM for 200% $\bar{g}_K$). It also changed the blocking concentration by >50% (1.30 mM for 40% $\bar{g}_K$, 0.82 mM for control, and 0.41 mM for 200% $\bar{g}_K$), as shown by the family of curves in Figure 4. Note that the rate of increase in latency with LA was steepest as the [LA] approached the C_b, an effect seen also in several of the biological fibers (Figure 2). Increasing the density of Na^+ channels ($\bar{g}_{Na}$) in the model had the effect of reducing slope sensitivity and of increasing the [LA] required to block conduction (dashed curve in Figure 4, where C_b nearly tripled for a 180% increase in $\bar{g}_{Na}$, with $\bar{g}_K$ at the normal value).

The range of slope sensitivities for latency (measured at $C_b/2$) in biological fibers was approximately fourfold (100% per mM to 414% per mM; Table 1; Figure 2). In model fibers with normal $\bar{g}_K$, varying Na^+-channel densities from 0.5 to 2 times the average (control) level, which is in accord with estimates for Na^+-channel densities based on differences among nodes under voltage-clamp (16,17), resulted in slope sensitivities ranging from 331% to 38% per mM, but always with a corresponding change in C_b. Thus, varying channel densities could account for interfiber differences observed in slope sensitivity, but not simultaneously for the independence of C_b.

Effects of Local Anesthetic on Activity Dependence

Membrane voltage and excitability normally undergo afteroscillations following propagation of an impulse, even in the absence of LA. These afterpotentials and excitability changes, which are reflected both in threshold and in latency, occur in central and peripheral axons (see Swadlow et al. [10] for review). The excitability changes are called "activity dependence." Activity dependence is prominent in frog sciatic fibers, where a short-term (<1 s) "superexcitable" phase (see control trace, Figure 5C), corresponding to a depolarizing afterpotential (18), and a longer lasting (several minutes) "depression" phase (Figure 6A) have been distinguished (7). In the intact frog fibers used here, we found that activity dependence was susceptible to low concentrations of LA.

Effects on superexcitability. In frog fibers, superexcitability is near its maximum 20 ms after the conditioning impulse (7). In these experiments, the firing threshold at this 20-ms delay after singlet conditioning pulses (CPs) was reduced by an average of 23.8% ± 6.9% (n = 29), with no LA present. A burst of impulses is known to produce a greater peak superexcitability than a single impulse does, and bursts of 8–10 impulses suffice to maximize this additive effect (7). Therefore, in these experiments maximal peak superexcitability was estimated by the peak superexcitability at the 20-ms delay after the last pulse of a 50-Hz burst of eight CPs and was approximately twice the peak superexcitability after singlet CPs, with the threshold descending by an average of 39.6% ± 19.2% (n = 25). After a 200-ms delay from a singlet CP, the threshold had usually increased from peak superexcitability to within 5%–10% of the resting threshold, but it was always at least slightly below the resting threshold at this delay, ranging from −1% to −28.5% (−8.8% ± 13.6%; n = 28). Stimulating at this 200-ms delay thus was a way of sampling membrane excitability during the recovery of superexcitability. By monitoring the threshold at

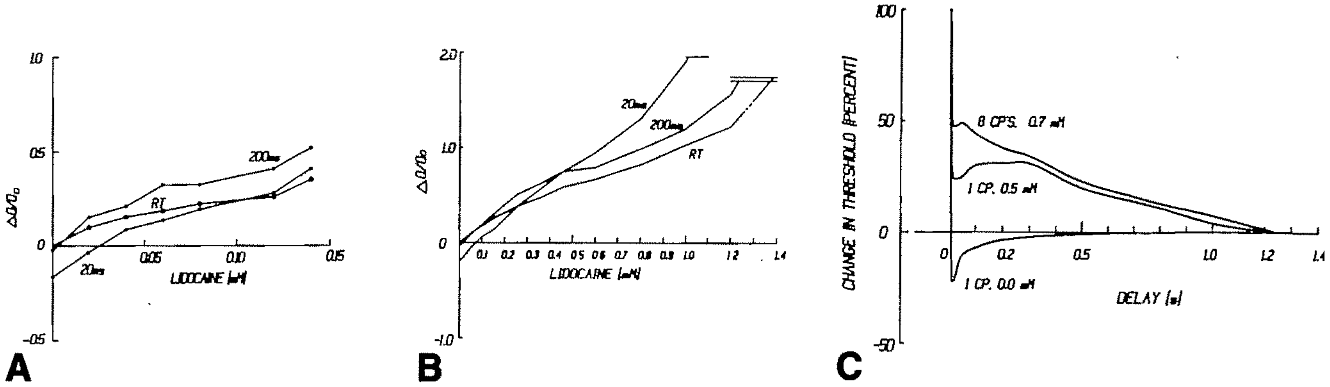

Figure 5. Effect of lidocaine on activity dependence. **A.** Threshold was expressed as the product of intensity and duration (i.e., the charge, Q, delivered) of stimuli at threshold level. The relative increase in threshold (change (Δ) in Q/resting threshold with no lidocaine, Q_0) is plotted after equilibration with 20 μM increments in lidocaine concentration. RT, curve for tonic threshold (threshold level stimuli given every 2 s); 20 ms, thresholds measured 20 ms after singlet conditioning impulses; and 200 ms, thresholds measured at that delay. In two nerves repeatedly exposed to 1 μM increments and washes, no effect on resting threshold was detectable below 10 μM, but superexcitability at 200 ms after an eight-pulse burst was reduced even at 1 μM by >25%. Five fibers exposed to 10 μM initial increments in concentration all showed increased thresholds at 200 and 20 ms after singlet conditioning pulses (CP) and eight-CP bursts. Conduction velocity (CV) = 23.6 m/s. **B.** Threshold versus lidocaine concentration as in **A** but for concentrations from 50 μM to blocking concentration(s). The 20-ms delay threshold shows initial superexcitability of 19.6%. The threshold at this delay crossed the tonic threshold at a lidocaine concentration of 0.25 mM and then crossed the 200-ms delay threshold at 0.37 mM. **C.** The "threshold curve" over the domain of delays from 0 (coincidence) to 1.4 s after conditioning impulses. These curves were plotted relative to the tonic resting threshold for the same fiber given 1 CP in the absence of lidocaine, for 1 CP after equilibration with 0.5 mM lidocaine, and for bursts of eight CPs with lidocaine at 0.7 mM. The progression with local anesthetic concentration from a pronounced superexcitability toward a curve with its highest relative threshold early after the impulse as seen here was consistent with similar plots at various concentrations made on 15 other fibers. CV = 21.1 m/s for part **B**; CV = 17.1 m/s for part **C**.

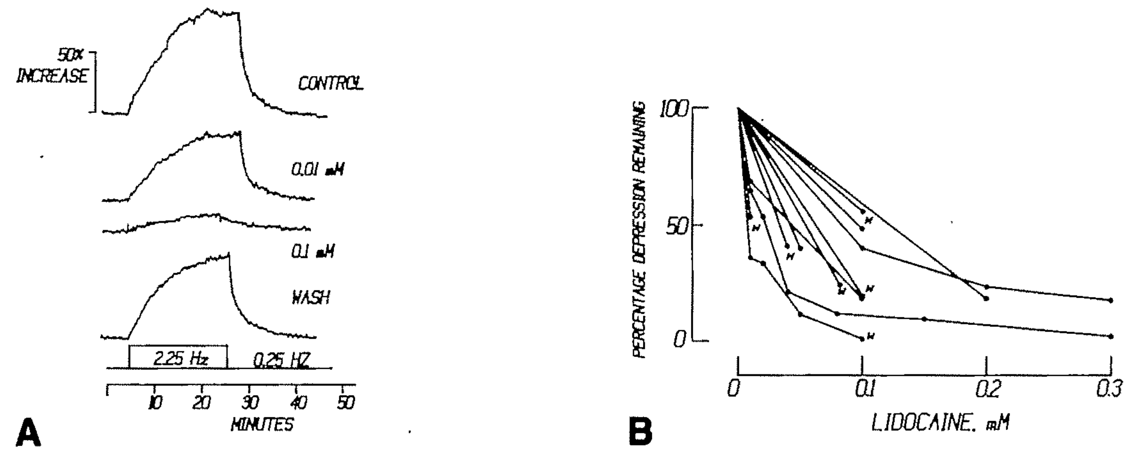

Figure 6. Reduction of depression by lidocaine. Depression was produced by stimulating conditioning bursts at three times threshold intensity. The bursts were timed so that the threshold tracking stimulus, which was given every 2 s, was delivered at a fixed interval >1.5 s after the last impulse of each repeated burst so that superexcitability (and use-dependent transients for lidocaine and 2-chloroprocaine, but not bupivacaine) had decayed. Records of the threshold tracking stimulus (example in part **A**) showed an initial resting level where only test stimuli were given. Then depression occurred, appearing as the buildup and plateau of threshold during the conditioning bursts, followed by a recovery tracked by test stimuli alone. When lidocaine was present, the degree of this depression was measured as the increase above the tonic level of threshold attained by the end of the period of increased impulse activity. This increase in threshold was plotted as the percentage of the increase in threshold seen without drug. Lidocaine reduced depression in all 12 fibers tested in this fashion (part **B**). Washing (W) with lidocaine-free solutions resulted in a recovery of depression; however, unless three or more solution changes were made over the course of several hours, depression was not restored to the control level. Experiments in which a conditioning profile was repeated at several concentrations of lidocaine (*connected data points*) showed a monotonic reduction in depression with concentration.

20- and 200-ms delay while increasing incrementally the lidocaine concentration, it was possible to make the first comparisons of the tonic effects of lidocaine with its phasic effects on the same fiber during the superexcitable phase after impulse activity. At low lidocaine concentrations (Figure 5A), lidocaine elevated the threshold at both the peak of superexcitability (20-ms delay, 1 CP) and during recovery

(200-ms delay, 1 CP) above the tonic "resting" threshold (no preceding impulse within 2 s). Thus, with lidocaine the fibers became transiently less excitable at delays where they would normally be superexcitable.

One way of quantifying the reduction of superexcitability with lidocaine was to determine an ED_{50}, a concentration where superexcitability was 50% of its control value after 1 CP. At the 20-ms delay, the ED_{50} for lidocaine was 107 ± 53 μM, ranging from 31 to 213 μM (n = 13), and at the 200-ms delay, the ED_{50} was 27 ± 22 μM, ranging from 2 to 82 μM (n = 15). As is apparent from the typical records in Figure 5, the tonic threshold increased less steeply with lidocaine than did the postimpulse threshold.

This transient subexcitability induced by lidocaine showed a typical sequence of "events" that could be marked as the concentration increased. At the lowest range of concentrations (21–150 μM, n = 11), the first such event was recorded when the threshold measured at the 200-ms delay crossed the elevated tonic level. The second event in the sequence was that the threshold at the 20-ms delay, corresponding without lidocaine to the peak of superexcitability, crossed the raised tonic level. The "crossing" concentration averaged 294 μM, ranged from 160 to 500 μM (n = 9), and was always greater in any given fiber than the concentration for the threshold at the 200-ms delay to cross the raised tonic threshold (Figure 5A and B). The third event occurred as the [LA] exceeded one-third or more of the C_b and was marked when the threshold at the 20-ms delay became even higher than at the 200-ms delay (Figure 5B). The last three events in the sequence were marked by conduction blocks. The order was consistently (n = 5) that the impulses at the 20-ms delay from a CP failed first, followed by failure of the impulse at the 200-ms delay, and finally by the tonic block of conduction in the fiber at the C_b. Failure of a test impulse (one preceded by a CP) thus occurs at concentrations less than required to produce tonic block and is an indication that a rising lidocaine concentration is approaching the C_b.

In addition to sampling the phasic effects at 20- and 200-ms delays from conditioning activity, plots of the threshold curve over the course of 1 s after CP(s) were made at several concentrations of lidocaine for each of 15 fibers (Figure 5C) to show the changed form of the afteroscillations in excitability. The results indicated that lidocaine has the effect of phasically elevating the postimpulse threshold, progressively transforming the curve as the concentration increased. At low concentrations, the afteroscillation remains one where the threshold is lowest at early delays and then rises before delaying again to the tonic steady-state level. At higher concentrations (e.g., 0.7 mM in Figure 5C), the threshold is highest at the earliest delays, declining progressively over the course of 1 s.

Effects on depression. Frog myelinated fibers differ among themselves in the degree of depression by a factor of >100 (19), but all fibers tested here showed a reduction in the level of depression when impulse activity occurred in the presence of lidocaine. Even 10 μM lidocaine could significantly reduce depression, and the ED_{50}, where fibers showed 50% of their predrug level of depression determined graphically from the data in Figure 6, was 58 ± 38 μM, ranging from 8 to 122 μM (n = 12). This was approximately 1/15th of the mean blocking concentration for fibers, as shown in Table 1 (880 μM). Bupivacaine (n = 7) and 2-chloroprocaine (n = 4) similarly reduced depression at concentrations well below the blocking dose (data not shown).

Effects of Impulse Activity on Local Anesthetic Actions

Activation of impulses in a fiber in the presence of LA also produces "use dependence," which is a different phenomenon from the activity dependence occurring in the absence of anesthetics. With threshold tracking, use dependence after a burst of firing appeared as a transient subexcitability that was strongly shaped by superexcitability. The magnitude of this transient subexcitability depended on both the burst frequency and the number of impulses in the burst (Figure 7), growing with either. It also depended on the agent. Stimulation at intervals of 2 s or more did not result in cumulative increases in threshold with either lidocaine or 2-chloroprocaine (Figures 5 and 7). However, with bupivacaine at concentrations ranging from 10 to 75 μM, the threshold measured by test stimuli separated by 5 s was invariably higher than it was when measured by stimuli at 10-s intervals (n = 8), and that at 2 s averaged 9.9% ± 1.6% more than the threshold at 20-s intervals for concentrations of 50 μM (n = 6).

The duration of the transient subexcitability, which should reflect the integration time for accumulation and recovery of LA-bound channels, was also agent specific (Figure 8A). Recovery of subexcitability after bursts of CPs in the presence of bupivacaine was marked by intervals of as much as 4 s, where no conducted impulse could be generated (Figure 8B). Return of excitability to the tonic threshold after this occluded interval was rapid, descending 200% or more in 200 ms. The occluded period followed a relative superexcitability that often permitted impulses to be conducted when stimulated at 20–50-ms

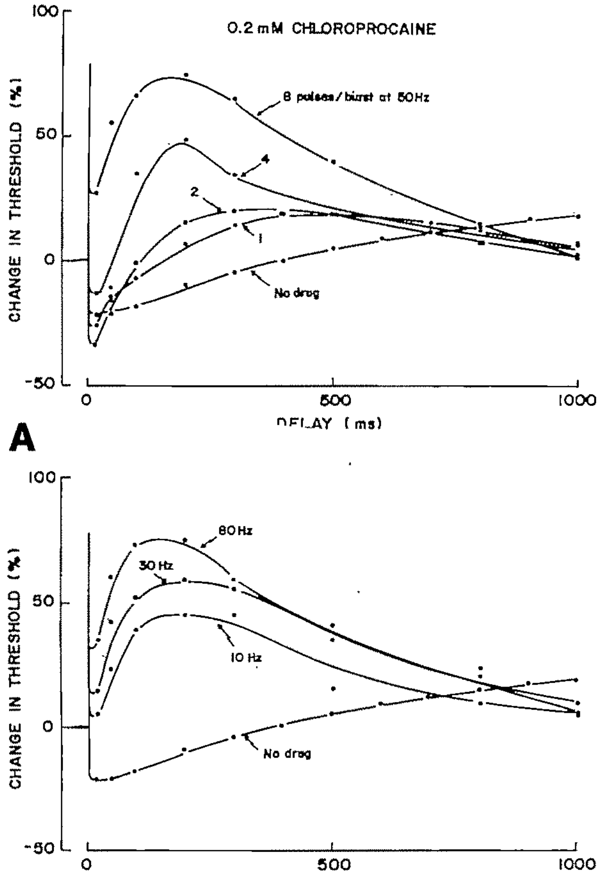

Figure 7. Use-dependent effects of 2-chloroprocaine on fiber excitability after short conditioning bursts. **A.** Effects of number of conditioning pulses (CP) at 20-ms intervals. Without drug, the fiber after one pulse is superexcitable for 800 ms (*No drug* trace in A and B), but after equilibration with 0.2 mM 2-choloroprocaine, the threshold relative to the steady-state level decreases only briefly after 1 CP by 25%, slightly less than the peak superexcitability (−32.8%) in the control trace. With more pulses, the transient subexcitability increases, peaking at 70% above the steady-state level at approximately 200 ms after a burst of eight conditioning pulses. The steady-state threshold is regained with 2-chloroprocaine within 1 s of the last CP, regardless of the degree of subexcitability. **B.** Effects of pulse frequency within a burst of eight conditioning impulses. The peak of the transient subexcitability increases monotonically with rate and is reached earlier after the last impulse: this would be expected if each impulse increased the proportion of bound Na$^+$ channels, which then recovered toward the tonic level between pulses.

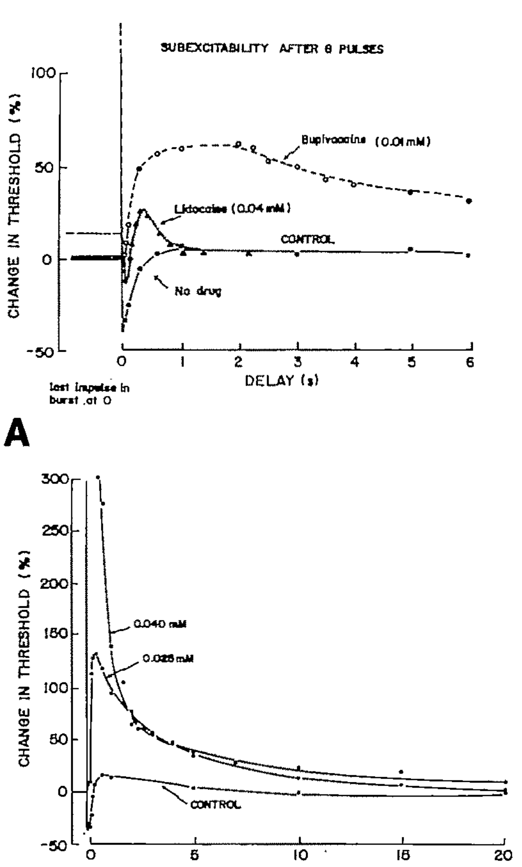

Figure 8. Subexcitability and use dependence with bupivacaine. **A.** Comparison of transient subexcitability with lidocaine versus bupivacaine in one fiber. The change in threshold is shown versus the delay from the last pulse of eight-pulse 50-Hz bursts. The bursts were given infrequently enough to avoid effects on resting threshold, and thresholds (plotted with respect to the drug-free resting level) were bracketed at various delays. Superexcitability was strong after eight pulses in the absence of local anesthetic (*No drug* trace). With lidocaine (40 μM), superexcitability was reduced, resting threshold increased approximately 5%, and a transient subexcitability occurred that recovered within 1 s. Bupivacaine (10 μM) was administered after lidocaine was washed twice for 34 min. The subexcitability with bupivacaine was greater and much more extended than with lidocaine. **B.** Dose dependence of subexcitability with bupivacaine after eight pulses. The change in threshold relative to the elevated tonic level is plotted versus delay from an eight-impulse 50-Hz burst. Note that at the 25 μM concentration, the peak of transient subexcitability was preceded by a pronounced relative superexcitability. At 40 μM, there was an occluded interval lasting 370 ms after the bursts. In nine fibers, four or eight pulse bursts given at concentrations >25 μM yielded intervals after the burst where stimuli three times the duration or twice the intensity could not fire another conducted impulse. An impulse could often be conducted at the 20-ms delay, which was why the bursts themselves were successful (eight conditioning pulses at 20-ms interpulse intervals), but for intervals ranging from 370 ms (shown here) to as much as 4 s (not shown) after the last pulse of a successful burst, one burst could prevent a following conducted impulse. Note the steep recovery of threshold after the occluded period with 40 μM bupivacaine.

delays from the burst but not afterward. Such occluded periods with abrupt recoveries were not observed after bursts in the presence of lidocaine (n = 19) or with 2-chloroprocaine (n = 3). They appeared in every fiber exposed to concentrations of ≥25 μM bupivacaine that could conduct intermittent eight-impulse 50-Hz bursts given at 30-s intervals (n = 9) (e.g., Figure 8B). In none of the three fibers exposed to tonic blocking concentrations of bupivacaine (range 140–400 μM) did the threshold at the 20-ms delay from a burst exceed that at the 200-ms delay as it did with lidocaine. Furthermore, in 15 fibers subjected to bupivacaine concentrations (range 5–100 μM) that did not cause conduction failures, the subexcitability at 200- or 300-ms delays always exceeded that at 20 ms, even after eight CP bursts, suggesting that a transiently increased excitability after a burst persists with bupivacaine but not with lidocaine. With lidocaine, the ED_{50} for peak superexcitability at 20 ms after eight CP bursts (40.1 ± 32.8 μM, range 17–111 μM, $n = 7$) was approximately half that after singlet CPs, reflecting the additive phasic blocking effects of the multiple CPs. With bupivacaine, the average ED_{50} for peak superexcitability after 1 CP was 25.9 μM (range 5.5–44.9 μM, $n = 5$), and it was 10.4 μM (range 1.7–44.3 μM, $n = 11$) after eight CP bursts. The threshold at 200- and 300-ms delays after an eight-CP burst was sensitive to bupivacaine, increasing an average of 51% above the tonic level in seven axons exposed to 10 μM bupivacaine and tested with eight CP bursts.

With 2-chloroprocaine, even at near-blocking concentrations, the threshold at a 20-ms delay never ($n = 4$) exceeded that at a 200-ms delay, as it invariably did with lidocaine (Figure 5). Thus, even though each agent produced a transient subexcitability after an impulse, the kinetic variables of that subexcitability were agent specific.

In frog fibers exposed to subblocking LA concentrations, conditions shown here to suppress activity dependence, the application of trains of electrical stimuli evoked surprising results. With bupivacaine, for example, stimulation at rates of one every 10 s to one every 2 s elicited responses to only every other or to every third stimulus, even over a broad range of stimulus intensities that were 100% successful if given at rates of one every 15 s ($n = 7$). With lidocaine, trains of 32 or 64 stimuli at >5 Hz led to impulse block that was either sporadic and intermittent or to a block that lasted indefinitely as long as the stimulus train itself continued, depending on rate and concentration (20).

Discussion

The principal actions of subblocking [LAs] observed on individually recorded frog fibers were (a) tonic increases of threshold and latency; (b) suppression of activity-dependent superexcitability and depression; and (c) transient subexcitability with agent-specific kinetics and duration following conditioning bursts of conducted action potentials. The results show that at low [LA], neuron intrinsic activity-dependent effects predominate in influencing impulse generation (threshold) and conduction, but as LA concentration increases, its agent-specific use-dependent properties will increase, becoming the dominant modulator of impulse conduction while the intrinsic activity-dependent processes decline because of the inhibiting effects of the agent on activity dependence.

Tonic Effects

Our results incorporated five interrelated but distinct measures of tonic susceptibility of fibers to LA. The first and most familiar is the critical blocking concentration (C_b), corresponding to the [LA] just sufficient to block impulse propagation through a region of nerve equilibrated with a homogeneous solution at a constant concentration. The C_b varied, even among fibers of the same resting conduction velocity, reflecting substantial intrinsic differences in susceptibility to block among axons of similar diameter (21). Two of the remaining measures, the maximal change in latency and the maximal change in threshold, revealed differences among axons in the range over which conduction variables could change in response to an impulse blocking dose of LA. These axonal differences were also not strongly correlated with C_b. The final two tonic measures were the slope-sensitivity measures of latency (Figure 2) and threshold (Figure 5) and revealed interaxonal differences in the degree that subblocking [LA] slowed the velocity of impulse propagation and diminished excitability at an exposed site.

Given that a fiber had relatively high slope susceptibility in latency one could reliably infer that it would also have a high slope susceptibility in threshold, but the C_b could not be predicted from either measure of the slope sensitivity. Some fibers with a moderately high slope sensitivity had such high margins of conduction safety that they nonetheless blocked at relatively high concentrations (Figure 2). The term conduction safety has several operational definitions (22,23) and refers to the current that an action potential provides that exceeds the current just necessary to sustain impulse propagation. Conduction safety is determined by anatomic and physiologic membrane properties governing impulse generation and propagation (e.g., channel type, density, locus, axoplasmic resistivity, membrane capacitance, degree of myelination, internodal spacing, ion concentrations), and we look to variations in these properties to explain axonal differences. Local anesthetics reduce conduction safety in two ways: they increase the current required to excite the local membrane, as shown by the threshold increases (24), and they reduce the current provided by the impulse because they block voltage-gated Na^+ channels. With lower affinity they also block voltage-gated K^+ channels (2), which, in the absence of a secondary depolarizing effect on the resting potential, will act to increase conduction safety by reducing the shunting of depolarizing current. Measuring C_b is thus in essence a measure of fiber conduction safety, and the differences in the maximal changes of threshold and latency among axons of similar C_b indicate that axons incorporate different combinations of the determinants of conduction safety.

Previous studies of C_b for single fibers at steady state for rabbit vagus nerve (4,25), bullfrog sciatic nerve (26), and cat saphenous nerve (3) also found a wide range of interfiber variation in C_b, either in the order in which single units blocked during onset of LA in vivo (3) or in the liminal concentration of LA after equilibration (4,27). In line with the conclusions of authors of previous work with single units, we believe that interfiber variation reflects biological variation from fiber to fiber in the determinants of conduction safety rather than artifacts introduced by dissection or physical injury. On three occasions we have recorded a single unit during exposure to a second sequence of lidocaine concentrations that resulted in a similar slope sensitivity and C_b, which has shown that susceptibility is stable in frog nerve fibers in vitro, at least for 1 or 2 days. Furthermore, we occasionally observed that fibers teased sequentially from the same nerve or recorded at the same time from a fascicle would show wide variation in susceptibility. We did not find that all fibers from a given nerve were of low susceptibility, whereas fibers from another (putatively injured nerve) were highly susceptible. The nerves were handled similarly and were not desheathed. A previous comparison among fibers from desheathed and sheath-intact vagal nerves found no significant differences in C_b (4), suggesting that the relatively substantial stretching and twisting associated with desheathing did not substantially affect conduction safety. Also, the average C_b found here for lidocaine (0.88 mM) was similar to the ED_{50} for the fastest conducting elevation of the frog sciatic compound action potential in bicarbonate-buffered solutions at 16°C (6), which would not be expected if many of the fibers used here had their intrinsic conduction safety reduced by damage.

Size Principle

The data from this population of myelinated frog axons is in accord with previous evidence from compound action potential studies and from studies with single fibers that have contradicted the idea, known as the "size principle," that susceptibility to block by LA is inversely related to axon diameter, as indicated by resting conduction velocity (4,28,29). Indeed, axon diameter, inferred from the resting conduction velocity before exposure to LA, does not seem to be related to any of the indices of susceptibility to LA that we used. A relation between critical blocking concentration and fiber size in 9 myelinated fibers was reported for bullfrog (26) but was not found in 16 unmyelinated or 22 myelinated fibers in rabbit vagus nerve (4) nor in multiple units recorded in dorsal root fascicles (3). Consideration of the implications of decremental conduction (30) for differential block (29) had previously led us to extend the idea of critical length (3) to pertain to LA exposure lengths of several centimeters (6). The results reported here for C_b correspond with results from rabbit vagus nerve, which were also obtained with at least 2 cm of nerve exposed to lidocaine, in showing that diameter cannot explain the differences in tonic susceptibility to conduction block with LA (4,25).

Impulse Slowing and Interfiber Variation

The tonic slowing of impulse propagation during exposure to LA is a well-established result and has been reported in several single-unit studies (3,4,27). The equilibration times observed here are consistent with times measured for slowing of impulse conduction to stabilize in vagal fibers with intact sheath in nerves exposed in vitro to stepwise increases in concentrations of lidocaine (31). As with frog fibers, the range of slope sensitivities in latency in a population of myelinated vagal fibers from rabbits was almost fivefold (Fink and Cairns [4; Figure 5]), although the magnitudes of slope sensitivities of the vagal fibers (180%–920% per mM) were approximately twice those of the frog fibers. The vagal fibers also blocked at approximately half the C_b of frog sciatic fibers (range 0.1–0.7 mM) (4). No plots of the slowing versus anesthetic concentration after equilibration have previously been published, however, and it is interesting to note how linear the relation is, only slightly convex (Figure 2A).

A nearly linear dependence of slowing on concentration also emerged in computer models of myelinated axons (Figure 4) in which node-to-node homogeneity in Na^+-channel density and internodal properties was assumed, suggesting that the linearity derives from the tonic reduction in the availability of voltage-gated channels by LA. In the model axon, adjusting the nodal density of K^+ channels (or the density of Na^+ channels) without changing any other variable yielded a range in C_b and in slope sensitivity for latency that included the range seen in the frog myelinated units studied here. Doubling the channel density and the internodal distance did not much affect (<11% change) the resting conduction velocity in a model fiber (32), although it altered the conduction safety. If biological fibers have independent control of their Na^+ and K^+ channel densities, then the modeling shows that channel densities alone could suffice to account for the observed fourfold span of slope sensitivities reported here. However, slope sensitivity in model fibers was always correlated with blocking concentration, and therefore at least one additional variable, such as internodal distance or axoplasmic resistivity, would need to be varied concomitantly with channel densities to produce a set of model fibers matching each of our biological fibers comprehensively in slope sensitivity, C_b, and maximal change in latency. In modeling impulse conduction in fibers, it is possible to preserve conduction safety by reducing the internodal distance while at the same time adjusting slope sensitivity to LA by altering the channel densities. This suggests one way that nerve fibers could achieve the observed independence between the C_b (dependent on internodal distance) and slope sensitivity (more dependent on the ratio of channel densities). Internodal distance is consistent along a given frog axon, but it varies between axons (19,21), which is consistent with this possibility.

Activity Dependence

The effects of LAs on activity dependence have not been widely studied in other laboratories (29,33). Examples of the inhibition of superexcitability and depression have been reported (15), and data here confirm that lidocaine decreases activity dependence in a dose-dependent manner in myelinated frog fibers. Activity-dependent excitability changes appear to be the axonal processes most sensitive to LAs, with effects appearing at low concentrations that produce little or no change in tonic excitability or conduction velocity. It has not yet been possible to study activity dependence in nodes of Ranvier under voltage-clamp or at the single-channel level, because expression of superexcitability and possibly of depression appears to require intact internodal structure.

Even at physiologically relevant discharge rates of two to eight impulses per second, depression is a powerful modulator of excitability and can more than double the intensity of a threshold level stimulus for some fibers (Figure 6A). As a stimulus of only half the resting threshold magnitude can result in an action potential during the superexcitable phase, the range of the afteroscillations in membrane excitability after an impulse can result in a fourfold change in the magnitude of a threshold level stimulus. These afteroscillations are thought to influence the distribution of impulses among branches in axonal presynaptic arborizations known as teledendra and to govern, at least in part, the discharge patterns for peripheral fibers encoding sensory stimuli or for central neurons encoding presynaptic influences (9,10). The information content of these discharge patterns could be affected by the suppression of activity dependence by low [LA] if the LA were present at peripheral receptors or terminal arborizations. As recognized by Larrabee and Posternak (34), the terminal arborizations of axons are probably areas of reduced conduction safety that would be more sensitive than trunk axons to anesthetics. If activity dependence normally controls the distribution of impulses in axonal teledendra (7,8,10), then LAs at low concentrations may affect information handling among neurons by dynamically altering the invasion of impulses in the terminal branches that precede the presynaptic endings, thus modifying temporal and spatial postsynaptic integration. At blood concentrations of lidocaine corresponding to those used here to suppress depression and superexcitability (10–30 μM), various "central" effects are reported, including dizziness and disorientation, suppression of seizures, drowsiness, analgesia, loss of ocular focus, tinnitis, muscle tremors, and at higher concentrations, seizures and generalized central nervous system depression (35). Whether inhibition of activity dependence is involved in the analgesic or sedative effects of systemic administration of LA (36) is not known, but the possibility should be considered, given the susceptibility of activity dependence to lidocaine on the order of 10–30 μM. Concerning general anesthesia, it has been suggested that afteroscillations in excitability may serve as the neurophysiologic substrate for consciousness by serving as a time-dependent process that puts each sequential impulse in a "context" of the pattern of discharge (37). The disorientation and periods of unconsciousness that occur during systemic lidocaine administration (38) may result from its action described here on activity-dependent processes, which could disrupt normal discharge patterns and suppress the substrate for this temporal context thought to be necessary for interpreting the patterns (37).

Depression has been shown to depend on the Na^+/K^+-dependent adenosine triphosphatase (9,39), and the inhibition of depression may result in part because the net ion transfer of Na^+ per impulse is diminished by LA, thus reducing the substrate driving the increased rate of ion pumping. A lidocaine concentration of 200 μM is sufficient to block approximately 30% of the Na^+ channels at rest in voltage-clamped nodes of Ranvier at 13°C (2,14,40). This mechanism is consistent with the reduction in central nervous system aerobic metabolism, of which a significant fraction is used to sustain ion gradients by metabolic pumping, by systemic LA at subconvulsant doses (41). Alternatively, reduced firing rates in central neurons may account for the reduced metabolism, although this familiar explanation does not seem to be supported by experimental tests for generalized reduction of firing throughout the brain during exposure to systemic LAs or even for exposure to general anesthetic agents.

Use Dependence and Transient Subexcitability

Use dependence in these experiments was revealed by novel measures that mapped the transient increases in threshold and in latency after impulse discharges. Unlike activity dependence, use dependence can be studied in voltage-clamp, where it appears as a phasic reduction of inward currents in voltage-clamped nodes of Ranvier subjected to repeated depolarizing pulses in the presence of LA (42,43). Use dependence underlies the progressive diminution of compound action potentials during trains of stimuli in nerves exposed to LA (11,44,45). Voltage-clamp studies have suggested that use dependence stems from increased binding of LA to Na^+-channel configurations that predominate during the membrane depolarization associated with the impulse, thus increasing the population of drug-bound channels and reducing the capability of the fiber to generate depolarizing currents needed to sustain propagation (2,14,46).

Modeling Use Dependence in Conducting Fibers

In conducting fibers, the membrane voltage before and during the action potential is affected by the LA rather than set by experimental equipment, as it is in voltage clamp. However, it is possible to quantitate the use-dependent effect on slowing and on propagation in mathematical models of uniformly conducting myelinated fibers, both for low discharge rates (no repeated spikes), as done here, and for trains of impulses (33) by using rate constants for forward and reverse binding measured for voltage-clamped amphibian nodes (14). In the model used here (Figure 4), it was assumed that the proportion of available channels in conformations with high affinity to LA is proportional to the instantaneous g_{Na} and that the effect of LA binding can therefore be simulated by reducing the variable for Na^+-channel density (maximal conductance, $\bar{g}_{Na}$). Action potentials in the model conduct at an appropriate rate and show good agreement in sensitivity of impulse conduction to [LA]. They give a good intuitive image of a conducting impulse in the region exposed to LA and provide the capability to explore the relative importance of particular structural or ionic properties in determining sensitivity of latency, threshold, and block to LA. In mathematical models of use dependence, impulse activity in the presence of LA can reduce conduction safety such that only the first propagated impulse in a sustained discharge can be conducted through the anesthetized axon (33). In fibers exposed to lidocaine, particularly after bursts of eight or more impulses rather than single conditioning pulses, the threshold after the last impulse in the burst decayed monotonically with no superexcitable dip, whereas in those fibers exposed to bupivacaine, the threshold after a burst always showed a large relative superexcitability (e.g., Figure 8B at 25 μM vs Figure 5B). The sharply different results in both scale and duration of transient subexcitability with low doses of lidocaine versus bupivacaine are consistent with experimental studies of use-dependent suppression of inward current (14,40). Nonconvulsing systemic doses of lidocaine also suppress ongoing "spontaneous" discharges originating at dorsal root ganglion cells in which the peripheral axons have been previously injured (47,48), and this effect may depend on its use-dependent actions as well as its tonic ones.

Local Anesthetic and "Functional Blockade"

Our findings indicate that the changes in membrane excitability that follow impulse conduction in unclamped fibers exposed to LA are a combination of use-dependent binding of LA, together with the inhibition of superexcitability and depression. These results show that the degree of LA blocking action that any particular impulse will be subjected to as it conducts through a region of axon exposed to LA will depend in agent-specific ways on its timing relative to preceding impulses, thus altering interval codes. For example, at concentrations yielding equivalent tonic effects, lidocaine ought to inhibit burst discharge with interpulse intervals ranging from 15 ms to several hundred milliseconds while allowing repeated discharge at 1 Hz without compromise, whereas bupivacaine might permit occasional, brief high-frequency bursts but block subsequent firing or conduction for several seconds. The possible relation of these disrupted discharge patterns to block of function is intriguing. Human volunteers given a partial block with lidocaine of medial or ulnar nerves such that Aδ fibers could be microneurographically recorded in response to low-frequency single shocks but not to repetitive trains nonetheless reported complete functional sensory loss of cold sensation in the region served by the nerve exposed to lidocaine (1). During the normal response of Aδ cold fibers to skin cooling, the fibers respond for several minutes at frequencies as high as 50 Hz (49), and we propose that infrequent discharges in tonically conducting but phasically inhibited fibers may not be functionally effective. Sustained electrical stimulation at subblocking concentrations of LA can result in a single conducted spike with all subsequent spikes blocked (33,50,51). These observations may explain how effective spinal and epidural block of sensory and motor functions may occur under conditions where infrequent impulses or volleys can nonetheless conduct to cerebral cortex (52).

Prospects for Differential Blockade

These methods are suited to ascertain relative fiber susceptibility, because they yield highly resolved measures for latency and excitability that can be monitored as a function of increasing concentration of LA, not simply one number of relatively low resolution giving the (tonic) C_b. Our results show that tonic C_b and phasic C_b differ. The tools may permit us to address the historic question of the relation of fiber susceptibility to fiber function and to do so with a link, via computer modeling, to the mechanistic basis of the differential susceptibilities.

We have thus formed the following four conclusions:

1. The afteroscillations in membrane excitability that normally follow impulse activity are the feature of conducting axons that is most susceptible to LAs. Lidocaine suppressed superexcitability by 50% at approximately 100 μM and depression by 50% at approximately 60 μM, concentrations less than one-tenth of the concentrations required to block impulse conduction in similar fibers.
2. Excitability following impulses was also distorted by the effects of use-dependent binding, which appeared as an agent-specific transient subexcitability.
3. These processes in tandem determined the likelihood of blockade of impulses, which occurred during high-frequency bursts at [LAs] one-third less than those needed for tonic blockade of infrequent impulses.
4. The increases in tonic threshold and latency grew in approximately linear proportion to [LA]. Interfiber differences in slope susceptibility and blocking concentration did not correlate with resting conduction velocity but were quantitatively similar to simulations of myelinated fibers differing in the membrane densities of voltage-gated ion channels.

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Central Nervous System Toxicity of Local Anesthetic Mixtures in the Rat

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Local anesthetics are often administered as mixtures during regional anesthesia. This study investigated whether a synergistic or antagonistic interaction between amide/amide or amide/ester local anesthetic combinations is present with respect to central nervous system toxicity. For surgical preparation, rats were anesthetized with 0.8% halothane in 30% O_2/balance N_2O and mechanically ventilated. Mean arterial blood pressure and the electroencephalogram were continuously monitored. After surgery, the halothane was discontinued for 15 min. An intravenous infusion of solutions containing lidocaine alone, bupivacaine alone, or any of three mixtures of the two drugs was then begun and continued at a fixed rate until seizure activity was observed on the electroencephalogram. Total administered doses of both drugs were compared by isobolographic analysis. After a similar protocol, a second experiment was performed evaluating lidocaine, tetracaine, or any of three mixtures of those two drugs. In both experiments, normocapnia, normoxia, and normothermia were maintained for all rats. For mixtures of lidocaine/bupivacaine ($P = 0.40$) and lidocaine/tetracaine ($P = 0.24$), there was no evidence that a significant degree of either synergism or antagonism was present. At the onset of seizures, mean arterial pressure was lowest in the lidocaine-alone groups in both experiments. Increasing doses of either bupivacaine or tetracaine (with correspondingly decreasing doses of lidocaine) were associated with greater mean arterial pressure values at onset of seizures. We conclude that central nervous system toxic effects of amide/amide or amide/ester anesthetic combinations, such as might occur during accidental intravascular injection, are no more than when the drugs are administered alone. Because such combinations appear to have additive epileptogenic effects, proportional reductions in the dose of one drug must be made if administered in combination with another.

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Local anesthetics are often administered as mixtures so as to combine the rapid onset of one anesthetic (e.g., lidocaine or tetracaine) with the prolonged duration of action of another (e.g., bupivacaine) (1,2). Several studies have examined the interaction of various local anesthetics with respect to systemic toxicity. Some work has found a synergistic relationship for toxicity between either amide/amide or amide/ester combinations (3,4). Other work has failed to support this conclusion (5–8). It is possible that differences in either toxicologic endpoints or physiologic conditions of experimental animals could account for these discrepancies. In this report, we provide additional evidence that, across a range of doses administered, local anesthetics are neither synergistic nor antagonistic with respect to central nervous system (CNS) toxicity.

Methods

After approval by the institutional Animal Care and Use Committee, male Sprague-Dawley rats (Harlan Sprague Dawley, Inc., Indianapolis, Ind.) were anesthetized with 4.0% halothane in O_2. A tracheostomy was performed, delivered halothane was reduced to 0.8% in 30% O_2/balance N_2O, and mechanical ventilation was begun using a small animal ventilator to maintain $Paco_2$ between 38 and 42 mm Hg and Pao_2 between 100 and 150 mm Hg. Catheters were surgically implanted in the right femoral artery and femoral vein. The arterial line was connected to a pressure transducer for monitoring of mean arterial blood pressure (MAP) while venous access was maintained

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for fluid and drug administration. *d*-Tubocurarine (0.4 mg) and heparin (100 *USP*) were administered intravenously. Electroencephalographic (EEG) needle electrodes (Grass type E2, Quincy, Mass.) were percutaneously inserted between the temporalis and parietal bones bilaterally, and a ground electrode was placed in the nape of the neck. Pericranial temperature was monitored from a needle thermistor (YSI model 524, Yellow Springs, Ohio) percutaneously positioned adjacent to the parietal bone and servoregulated to 37.0°C by a heat lamp. Forty-five minutes after induction of anesthesia, halothane was discontinued and the inspiratory gas mixture changed to 70% N_2O/30% O_2. A 15-min stabilization period was then allowed, during which time $Paco_2$, Pao_2, arterial pH (pHa), and hematocrit (Hct) were determined.

Test for Lidocaine-Bupivacaine Interaction

Stock solutions of either 1.5% lidocaine HCl, prepared by diluting 2.0% Xylocaine (Astra, Westborough, Me.) in 0.9% NaCl, or 0.5% bupivacaine HCl (0.5% Sensorcaine, Astra) were used. The local anesthetic concentrations for each of the two stock solutions were derived from pilot studies that demonstrated that either solution, administered at the same infusion rate, would produce seizures within 13–18 min after onset of infusion. From these stock solutions, five solutions were prepared. With the investigator unaware of experimental conditions, rats were assigned by chance to one of five groups distinguished by the solution administered: group I (lidocaine alone) received 15.0 mg/mL of lidocaine (n = 10); group II (lidocaine + bupivacaine [6:1 mg]) received a 2.0:1.0-mL mixture of the stock solutions (yielding lidocaine 10.0 mg/mL and bupivacaine 1.6 mg/mL) (n = 11); group III (lidocaine + bupivacaine [3:1 mg]) received a 1.0:1.0-mL mixture of the stock solutions (yielding lidocaine 7.5 mg/mL, bupivacaine 2.5 mg/mL) (n = 10); group IV (lidocaine + bupivacaine [3:2 mg]) received a 1.0:2.0-mL mixture of the stock solutions (yielding lidocaine 5.0 mg/mL, bupivacaine 3.3 mg/mL) (n = 11); and group V (bupivacaine alone) received 5.0 mg/mL of bupivacaine (n = 10). In each group, the solution was infused intravenously at a constant rate of 0.0016 $mL \cdot g$ body $wt^{-1} \cdot min^{-1}$. During surgery, all wounds had been subcutaneously infiltrated with the same solution to be infused for the respective groups (0.4 mL total).

Fifteen minutes after discontinuation of halothane, the respective infusions were begun. The EEG was continuously monitored beginning 5 min before the onset of infusion (Grass model 8-10c). At the onset of EEG seizures, marked by the appearance of high-voltage spike-wave activity, MAP was recorded, and arterial blood (5 mL) was withdrawn. The $Paco_2$, Pao_2, pHa, and MAP were determined. Plasma was frozen for later determinations of lidocaine and bupivacaine concentrations by gas chromatography. The duration of infusion (min) before onset of seizures and total dose of each local anesthetic administered (mg/kg) were recorded.

Test for Lidocaine-Tetracaine Interaction

The surgical preparation and experimental protocol for this study were exactly as described previously (test for lidocaine-bupivacaine interaction), except that in this experiment combinations of lidocaine and tetracaine were evaluated. Stock solutions of either 1.5% lidocaine HCl, prepared by diluting 2.0% Xylocaine (Astra) in 0.9% NaCl, or 0.375% tetracaine HCl, prepared by dissolving 20 mg of Pontacaine (Winthrop Pharmaceuticals, New York, N.Y.) in 5.33 mL of 0.9% NaCl, were used. The local anesthetic concentrations for each of the two stock solutions were derived from pilot studies that demonstrated that either solution, administered at the same infusion rate (0.0016 $mL \cdot g$ body $wt^{-1} \cdot min^{-1}$), would produce seizures within 13–18 min after onset of infusion. From these stock solutions, five solutions were prepared for intravenous infusion. With the investigator unaware of the experimental conditions, rats (n = 10) were assigned by chance to one of five groups distinguished by the intravenous solution administered. In this experiment, plasma concentrations of the local anesthetic agents at onset of seizures were not determined: group I (lidocaine alone) received 15.0 mg/mL of lidocaine; group II (lidocaine + tetracaine [8:1 mg]) received a 2.0:1.0-mL mixture of the stock solutions (yielding lidocaine 10.0 mg/mL, tetracaine 1.3 mg/mL); group III (lidocaine + tetracaine [4:1 mg]) received a 1.0:1.0-mL mixture of the stock solutions (yielding lidocaine 7.5 mg/mL, tetracaine 1.9 mg/mL); group IV (lidocaine + tetracaine [2:1 mg]) received a 1.0:2.0-mL mixture of the stock solutions (yielding lidocaine 5.0 mg/mL, tetracaine 2.5 mg/mL); group V (tetracaine alone) received 3.7 mg/mL of tetracaine.

Statistical Methods

Scaf's test for drug interaction was used (9). The ratio of the potency of the two drugs was estimated from the ratio of the geometric means of groups I and V. Scaf's test converts the isobolic analysis of drug interaction (10) to a one-way analysis of variance (ANOVA). The SYSTAT software package was used to perform the statistical analysis (11,12). Standard tests of the assumptions of ANOVA were performed, with the criteria for statistical significance of $P < 0.01$.

Table 1. Physiologic Values Measured Before Anesthetic Infusion and at the Onset of Seizures (Test for Lidocaine-Bupivacaine Interaction)

	Group I (lidocaine alone)	Group II (lidocaine + bupivacaine [6:1 mg])	Group III (lidocaine + bupivacaine [3:1 mg])	Group IV (lidocaine + bupivacaine [3:2 mg])	Group V (bupivacaine alone)
Preinfusion					
MAP (mm Hg)	111 ± 13	113 ± 19	109 ± 11	114 ± 11	114 ± 14
Pao_2 (mm Hg)	108 ± 11	115 ± 12	123 ± 15	124 ± 26	124 ± 14
$Paco_2$ (mm Hg)	39 ± 3	39 ± 3	39 ± 4	38 ± 3	39 ± 2
pHa	7.41 ± 0.03	7.43 ± 0.03	7.40 ± 0.02	7.43 ± 0.02	7.40 ± 0.02
Hematocrit (%)	39 ± 3	42 ± 3	39 ± 2	41 ± 2	39 ± 3
Body weight (g)	330 ± 34	336 ± 16	346 ± 21	342 ± 17	339 ± 19
Onset of seizures					
MAP (mm Hg)	99 ± 22	122 ± 24	119 ± 26	143 ± 30	156 ± 22
Pao_2 (mm Hg)	107 ± 20	111 ± 14	122 ± 24	126 ± 34	126 ± 19
$Paco_2$ (mm Hg)	39 ± 5	40 ± 4	39 ± 3	42 ± 3	38 ± 2
pHa	7.39 ± 0.04	7.42 ± 0.03	7.43 ± 0.03	7.39 ± 0.02	7.42 ± 0.02
Cranial temp. (°C)	37.1 ± 0.3	37.0 ± 0.2	37.0 ± 0.1	37.0 ± 0.2	37.0 ± 0.1

MAP, mean arterial blood pressure; pHa, arterial pH; temp., temperature.
Values are mean ± SD.

Probability plots and Lilliefors tests showed that the residuals followed a normal distribution. By Bartlett's test, the variance of the residuals did not differ among groups. Plots of residuals against estimated doses showed no evidence for dependence. None of Cook's distances were statistically significant. One of the 102 studentized residuals was statistically significant (3.204); however, review of physiologic measurements revealed no basis for rejecting the datum. Furthermore, repeat of the ANOVA without the datum (not shown) did not change the results qualitatively. Power analysis was performed by routine methods for ANOVA (13); $\alpha = 0.05$ and $n = 10$ were assumed to hold for each group. As is appropriate for Scaf's method, the number of between-group degrees of freedom was set to equal 3. Each lidocaine dose was corrected for its corresponding bupivacaine dose using the estimated potency ratio. Then, the antilogarithm of (the root-mean-squared deviation of [the group mean log-corrected lidocaine doses about the grand mean log-corrected lidocaine dose]) was calculated. Scaf's method uses ANOVA on the logarithms of the doses. Therefore, the results of the power analysis are reported as ratios.

The MAP values were analyzed by one-way analysis of covariance, with covariance the baseline MAP. Standard assumptions were tested and satisfied, as described in the preceding paragraph. One MAP value had a statistically significant studentized residual (−4.34). This outlier was not included in the analysis.

Results

Test for Lidocaine-Bupivacaine Interaction

Physiologic values before the start of local anesthetic infusion and at the onset of seizures are reported in Table 1. Values for Pao_2, $Paco_2$, pHa, and Hct were within the normal range. The MAP was similar among groups before onset of infusion. In contrast, at onset of seizures, MAP values differed among groups ($F[4,45] = 12.7$; $P = 5.5 \times 10^{-7}$). The MAP values were substantially greater in the bupivacaine alone (156 ± 22 mm Hg) versus lidocaine alone (99 ± 22 mm Hg) groups, whereas MAP values in the various local anesthetic mixture groups were intermediate.

Examples of typical EEG activity at different phases of the experiment are provided in Figure 1. The duration of local anesthetic infusion necessary to produce seizures is reported in Table 2. The mean duration of drug infusion in the lidocaine-alone group (17.0 min) was 3.5 min greater than in the bupivacaine-alone group (13.5 min). As intended, the total doses of lidocaine and bupivacaine differed among groups based on the infusion regimen. Total doses of lidocaine and bupivacaine required to produce seizures in individual rats are plotted in Figure 2. The isobolic line is shown, indicating predicted values for additivity. Doses of lidocaine and bupivacaine administered in combination fell on both sides of the isobolic line. There was no statistical evidence for an interaction between the two

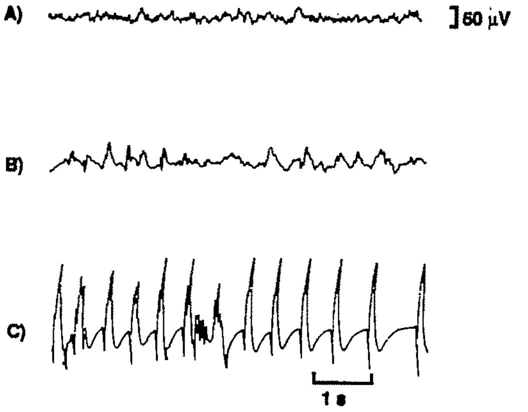

Figure 1. EEG tracings during the experiment: (**A**) typical EEG activity before the start of lidocaine infusion (during 70% nitrous oxide/trace halothane analgesia); (**B**) during lidocaine infusion but before onset of seizure activity; (**C**) seizure activity.

anesthetic agents with respect to epileptogenesis (F[3,47] = 1.00; P = 0.401). A power of 0.80 was present to detect a 10% deviation of mean lidocaine doses from the isobolographic line. For both lidocaine and bupivacaine, larger doses of both anesthetics were associated with greater plasma concentrations, respectively (Figure 3).

Test for Lidocaine-Tetracaine Interaction

Physiologic values before and at the onset of seizures are listed in Table 3. Values for Pa_{O_2}, Pa_{CO_2}, pHa, and Hct were within the normal range. The MAP was similar among groups before onset of infusion. In contrast, at onset of seizures, MAP values differed among groups (F[4,44] = 9.62; $P = 1.1 \times 10^{-5}$). The MAP values were substantially greater in the tetracaine alone (137 ± 18 mm Hg) versus lidocaine alone (73 ± 23 mm Hg) groups, whereas values in the local anesthetic mixture groups were intermediate.

For this experiment, total doses of lidocaine and tetracaine administered at the onset of seizure activity (Table 4) are plotted along with the isobolic line in Figure 4. Less uniformity in the distribution of values is evident than was the case with lidocaine-bupivacaine combinations. Nevertheless, there was no evidence for an interaction between these two agents (F[3,45] = 1.47; P = 0.24). A power of 0.80 was present to detect a 10% deviation of mean lidocaine doses from the isobolographic line.

Discussion

The question as to whether local anesthetics interact is not new. As early as 1912 investigations were carried out to determine whether synergism for potency could be obtained with mixtures of local anesthetics (14). Later work focused on the potential for synergistic toxicity. The first such study identified a more rapid onset of cardiac arrest in rats that had received intravenous infusions of a mixture of 1.0% lidocaine and 0.1% tetracaine versus 1.0% lidocaine alone. However, the effect of tetracaine was absent if combined with 1.5% lidocaine, indicating that significant interactions between local anesthetics might be manifest only within specific ranges of a dose-response curve (4). This conclusion was supported by the work of Brecher et al. (6) who demonstrated, with intraperitoneal injections of lidocaine-tetracaine combinations in mice, that toxicity (mortality) varied significantly with different doses of each drug.

The significance of these interactions can be questioned, however, given the reported broad clinical experience with combinations of local anesthetics for regional anesthesia. In a retrospective study of 10,538 patients who received mixtures of local anesthetics for regional anesthesia, systemic toxicity was observed in only 10 cases (<0.1%) (2).

More recent animal studies are consistent with that clinical experience. Munson et al. (8) measured EEG activity during either a rapid or slow intravenous bolus dose of a fixed ratio of lidocaine-etidocaine or lidocaine-tetracaine administered in rhesus monkeys. That study concluded that mixtures of lidocaine-etidocaine or lidocaine-tetracaine, in proportions equal in potency, have approximately the same epileptogenic potential as either drug administered alone. Those results are convincing but limited in interpretation, because only one mixture of either combination of drug was evaluated. De Jong and Bonin (7) provided further evidence for lack of toxic interaction between local anesthetics by determining the median convulsant dose and median lethal dose for bupivacaine, lidocaine, and choloroprocaine administered independently by subcutaneous injection in mice. Mixtures of these drugs were again found to be no more convulsant or lethal than the parent components administered alone.

Our approach to the question of CNS toxicity from combinations of local anesthetics offers several methodologic improvements over previous studies. First, a variety of doses were evaluated by isobolographic analysis for each pair of drugs. Thus, the possibility that an interaction might be present at one point on the dose-response curve but absent at another could be directly evaluated. Second, the effects of these combinations were monitored on the EEG, perhaps providing a more discrete toxicologic endpoint than motor convulsions (7). Indeed, this may have been successful, because the coefficients of variation for epileptogenic doses in our study (lidocaine 16%; bupivacaine 17%; tetracaine 21%) were approxi-

Table 2. Durations of Infusion, Total Doses, and Plasma Concentrations of Local Anesthetics at Onset of Electroencephalographic Seizures (Test for Lidocaine-Bupivacaine Interaction)

	Group I (lidocaine alone)	Group II (lidocaine + bupivacaine [6:1 mg])	Group III (lidocaine + bupivacaine [3:1 mg])	Group IV (lidocaine + bupivacaine [3:2 mg])	Group V (bupivacaine alone)
Duration of infusion (min)	17.0 ± 1.8	15.5 ± 3.2	16.3 ± 2.5	15.3 ± 3.4	13.5 ± 2.0
Lidocaine dose (mg/kg)	41.4 ± 6.6	23.9 ± 5.0	19.1 ± 2.9	12.3 ± 2.3	0
Bupivacaine dose (mg/kg)	0	3.9 ± 0.9	6.4 ± 1.0	7.8 ± 2.0	10.7 ± 1.8
Lidocaine plasma concentration (µg/mL)	7.8 ± 1.4	5.3 ± 0.9	3.9 ± 1.2	2.7 ± 0.3	0
Bupivacaine plasma concentration (µg/mL)	0	0.7 ± 0.4	1.0 ± 0.4	1.4 ± 0.7	3.1 ± 1.3

Values are mean ± SD.

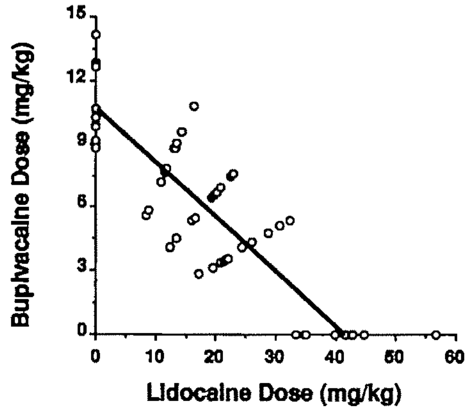

Figure 2. Lidocaine and bupivacaine were administered intravenously either alone or in fixed-ratio doses. Individual values for total doses of lidocaine or bupivacaine, or both, administered at the onset of EEG seizures are depicted. The isobolic line (predicted line of additivity) is provided. As can be observed, the data appear to be equally distributed on both sides of the isobolic line, excluding the possibility of either an antagonistic or synergistic interaction between these two anesthetics.

mately one-half those observed when motor convulsions were previously used as an endpoint for observing epileptogenicity (7). Third, MAP changes associated with CNS toxicity were monitored. Finally, ventilation was supported, thus avoiding any effect of anesthetic-induced respiratory depression on the results (15).

The one limitation of our preparation was the coadministration of nitrous oxide and halothane. To minimize EEG artifacts, spontaneous movement could not be allowed; thus, paralytic agents (*d*-tubocurarine) and appropriate sedation were required. Nitrous oxide has been demonstrated to increase the threshold for lidocaine-induced seizures (16). Halothane, in large doses, has been recognized as an anticonvulsant for status epilepticus (17). We sought to minimize the halothane effect by discontinuing it 15 min before onset of local anesthetic infusion (effectively constituting 30 min before onset

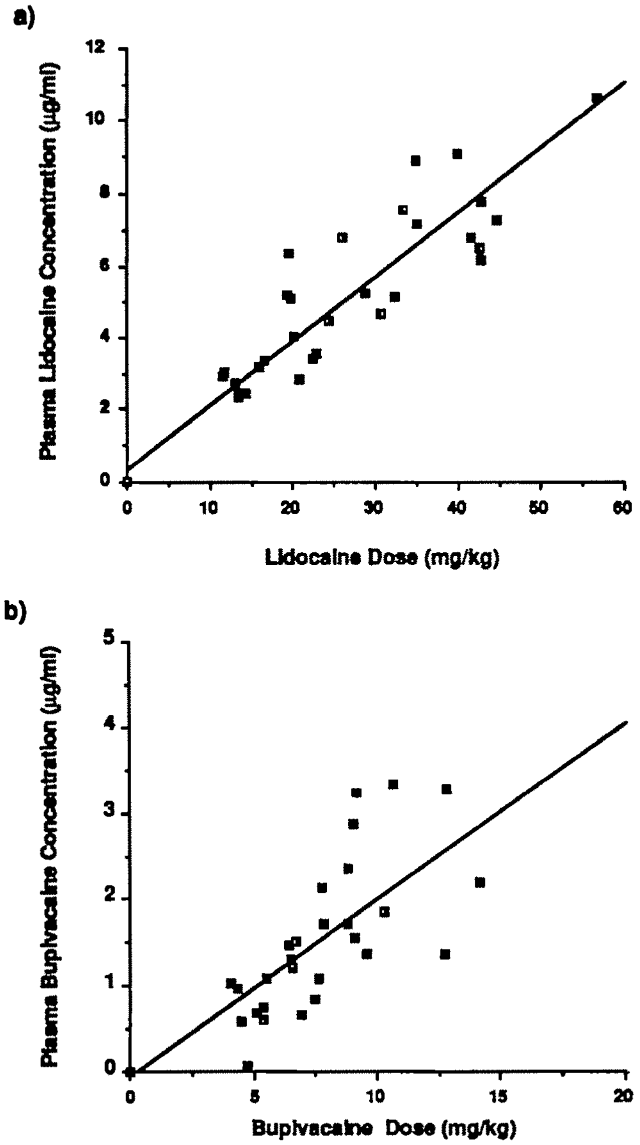

Figure 3. (a) Scattergram of plasma lidocaine concentration versus total dose of lidocaine administered at the onset of seizures; a *best-fit line* is provided. (b) Scattergram of plasma bupivacaine concentration versus total dose of bupivacaine administered at the onset of seizures; a *best-fit line* is provided.

Table 3. Physiologic Values Measured Before Anesthetic Infusion and at the Onset of Seizures (Test for Lidocaine-Tetracaine Interaction)

	Group I (lidocaine alone)	Group II (lidocaine + tetracaine [8:1 mg])	Group III (lidocaine + tetracaine [4:1 mg])	Group IV (lidocaine + tetracaine [2:1 mg])	Group V (tetracaine alone)
Preinfusion					
MAP (mm Hg)	114 ± 14	117 ± 11	115 ± 14	123 ± 11	107 ± 10
Pa_{O_2} (mm Hg)	120 ± 26	141 ± 27	124 ± 26	132 ± 13	124 ± 19
Pa_{CO_2} (mm Hg)	40 ± 2	40 ± 6	39 ± 3	40 ± 3	39 ± 3
pHa	7.43 ± 0.03	7.43 ± 0.06	7.44 ± 0.02	7.44 ± 0.03	7.43 ± 0.01
Hematocrit (%)	42 ± 2	43 ± 3	42 ± 3	43 ± 2	42 ± 2
Body wt (g)	318 ± 18	325 ± 21	314 ± 10	322 ± 24	330 ± 10
Onset of seizures					
MAP (mm Hg)	73 ± 23	74 ± 23	89 ± 33	99 ± 38	137 ± 18
Pa_{O_2} (mm Hg)	122 ± 21	134 ± 23	118 ± 21	127 ± 15	125 ± 18
Pa_{CO_2} (mm Hg)	41 ± 1	37 ± 4	41 ± 3	39 ± 4	39 ± 3
pHa	7.43 ± 0.03	7.45 ± 0.03	7.43 ± 0.03	7.44 ± 0.06	7.46 ± 0.11
Cranial temp. (°C)	37.0 ± 0.1	37.0 ± 0.1	37.0 ± 0.1	37.0 ± 0.1	37.0 ± 0.1

MAP, mean arterial blood pressure; pHa, arterial pH; temp., temperature.
Values are mean ± SD.

Table 4. Durations of Infusions and Total Doses of Local Anesthetics Administered at Onset of Electroencephalographic Seizures (Test for Lidocaine-Tetracaine Interaction)

	Group I (lidocaine alone)	Group II (lidocaine + tetracaine [8:1 mg])	Group III (lidocaine + tetracaine [4:1 mg])	Group IV (lidocaine + tetracaine [2:1 mg])	Group V (tetracaine alone)
Duration of infusion (min)	17.3 ± 2.5	16.7 ± 3.8	17.8 ± 2.3	15.1 ± 3.0	15.3 ± 2.3
Lidocaine dose (mg/kg)	40.2 ± 5.7	26.5 ± 5.8	20.6 ± 2.6	11.7 ± 2.3	0
Tetracaine dose (mg/kg)	0	3.2 ± 0.7	5.3 ± 0.7	5.8 ± 1.1	8.9 ± 1.2

Values are mean ± SD.

of seizures). At this interval, in a separate group of otherwise identically treated rats, we measured an end-tidal halothane concentration of 0.15% ± 0.06%. The presence of nitrous oxide and trace halothane, although presumably similar across groups, undoubtedly provided some anticonvulsant activity, explaining in part the large doses of local anesthetic required to produce epileptic activity.

The results from our study are consistent with the conclusions drawn by Munson et al. (8) and de Jong and Bonin (7). Across a wide dosage range of combinations of either amide-amide or amide-ester local anesthetics, no evidence for either synergism or antagonism could be detected. These findings, along with the clinical safety and efficacy reported for combinations of local anesthetics in regional anesthesia (2), provide considerable support for the continuation of this practice when indicated by clinical conditions.

The MAP effects of the local anesthetic doses

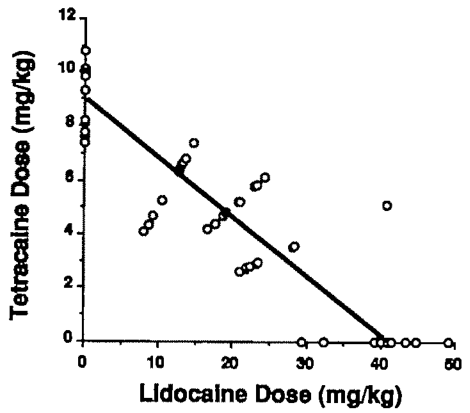

Figure 4. Lidocaine and tetracaine were administered intravenously either alone or in fixed-ratio doses. Individual values of total doses of lidocaine or tetracaine, or both, administered at the onset of EEG seizures are depicted. The *isobolic line* (predicted line of additivity) is provided. As can be observed, the data appear to be equally distributed on both sides of the isobolic line (predicted line of additivity), excluding the possibility of either an antagonistic or synergistic interaction between these two anesthetics.

necessary to cause seizures were somewhat unexpected. In both experiments, the lowest MAP values at onset of seizures were observed in the lidocaine-alone groups. Reduction of the lidocaine dose, by increasing either the bupivacaine or tetracaine dose, ameliorated this effect. De Jong and Bonin (7) similarly observed that the mixtures of lidocaine with bupivacaine or lidocaine with chloroprocaine were less likely to produce death, presumably from cardiovascular collapse, in mice without ventilatory support. Our experiment was discontinued after onset of seizure activity but before hemodynamic collapse became evident. This protocol was established because of the potential confounding influence of drawing blood samples, at the onset of seizures, on subsequent hemodynamic events. Because bupivacaine has been demonstrated to exhibit a narrow margin of safety between onset of convulsions and cardiovascular collapse (18), further work specifically addressing this issue is necessary to allow the conclusion that mortality from local anesthetic overdoses can be reduced by using a combination of local anesthetics as opposed to one anesthetic alone. Further, our observations may be specific to the rat, given the relatively high heart rate found in this species (250–350 beats/min). Because the cardiotoxic effect of local anesthetics is heart-rate dependent (19), observations made in this study may not be relevant in humans, who characteristically have a slower heart rate.

We conclude that the CNS toxic effects of amide-amide or amide-ester anesthetic combinations, such as might occur during accidental intravascular injection, are no greater than when the respective anesthetics are administered alone in the rat. However, because such combinations appear to be additive with respect to CNS toxic effects, proportional reductions in the dose of one anesthetic must be made if administered in combination with another.

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Locomotor Activity After Recovery From Hypnosis: Midazolam-Morphine Versus Midazolam

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This study was performed to test the hypothesis that sedation after recovery from pharmacologic hypnosis is less pronounced if hypnosis is induced with a midazolam-morphine combination compared with midazolam administered alone. Loss of the righting reflex was used as an index for the hypnotic effect and reduction of locomotor activity as an index for the sedative effect. One group of rats received midazolam (20 mg/kg IV) and another group an equipotent (in relation to the hypnotic effect) combination of midazolam (4 mg/kg IV) and morphine (1.3 mg/kg IV). The duration of loss of the righting reflex in the midazolam and midazolam-morphine groups was 30 ± 3 and 28 ± 2 min, respectively (mean ± SE). The difference between the groups in locomotor activity after recovery from hypnosis was very pronounced. The locomotor activity in the midazolam-morphine group at 1 and 2 h was seven and five times greater, respectively, than in the midazolam group ($P < 0.005$). The profound difference in locomotor activity for the two treatment groups was explained on the basis of the difference in the outcomes of midazolam-morphine interactions with regard to hypnosis (synergism) and sedation (summation). When the animals recovered from hypnosis, the synergism of the drug interaction ceased to be a contributing factor.

(Anesth Analg 1992;75:929–31)

Benzodiazepine-opioid hypnotic interaction for induction of unconsciousness in patients was found to be synergistic (supraadditive) (1). Experiments in rats also demonstrated that the diazepam-morphine (2) or midazolam-morphine (3) interactions for pharmacologic hypnosis (4) (loss of the righting reflex index) are highly synergistic. However, when the midazolam-morphine interaction was studied in rats with regard to sedative effect (inhibition of locomotor activity index), instead of the expected synergism, we found a simple summation of the effects (3). Doses of midazolam necessary for sedation are manyfold smaller than those for hypnosis. There is a possibility that when midazolam-morphine synergism develops with high (hypnotic) doses, it would also continue to exist for sedation after recovery from hypnosis. An assessment of the drug interactions for two actions, hypnotic and sedative, in the same experiment when one of the actions is followed by another, would examine this possibility.

The present study was designed to test the following hypothesis: sedation after recovery from midazolam-induced hypnosis should be more pronounced than sedation after hypnosis induced by a midazolam-morphine combination, because when animals recover from the latter, the synergism of drug interaction ceases to be a contributing factor.

Methods

Experiments were performed in 66 male Sprague-Dawley rats weighing 225–275 g. The protocol for this study was approved by the Institutional Panel on Laboratory Care. As an index for hypnotic effect, we used the loss of the righting reflex; as an index for sedative effect, the reduction of locomotor activity. The righting reflex was tested in the following way: the rat was placed in a cylindrical, revolving cage with its paws down; the cage was rotated (1 revolution/15 s) to place the rat on its back, after which the rotator was stopped for 15 s. If the rat could not be placed on its back for 15 s, or could not remain on its back for an additional 15 s, the righting reflex was considered not blocked.

Spontaneous locomotor activity was measured with the use of an activity meter (Opto-Varimex-Mini, Columbus Instruments, Columbus, Ohio) that counted the number of infrared beam interruptions (15 beams with sensors equally spaced [2.65 cm] in the cage at a distance of 5.25 cm from the floor.) Only

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ambulatory activity was taken into account; stereotypic movements that caused rapid, repeated interruptions of the same beam (e.g., grooming, digging, scratching) were not considered. Each rat was placed into the activity cage alone, and only once, for 15 min.

Midazolam or a combination of midazolam and morphine was administered intravenously into the saphenous vein. The selected drug doses provided equipotency with regard to hypnotic effect. We used midazolam (20 mg/kg) and an equipotent combination of 4 mg/kg of midazolam and 1.3 mg/kg of morphine (doses according to a previous study [3]). In the combined drug experiments, each drug was injected separately, with an interval of 12 min to synchronize its peak effect.

The righting reflex was determined every 5 min. After recovery of the righting reflex, a rat's locomotor activity was determined at different time intervals in different subgroups of animals. Both midazolam and midazolam-morphine groups had five subgroups of six animals, with locomotor activity determinations at 1, 2, 4, 8, or 16 h after drug administration. A control group receiving no drugs was used for comparison. Morphine sulfate was obtained from Eli Lilly Co. (Indianapolis, Ind.) and midazolam hydrochloride from Roche Laboratories (Nutley, N.J.).

The locomotor activity (beam crossing) was summarized as the mean ± SE. For comparisons of the mean number of beam crossings, a two-way analysis of variance was used (5). Pairwise tests between any two means utilized Fisher's protected least significant difference test (5). Differences were declared statistically significant if $P < 0.05$.

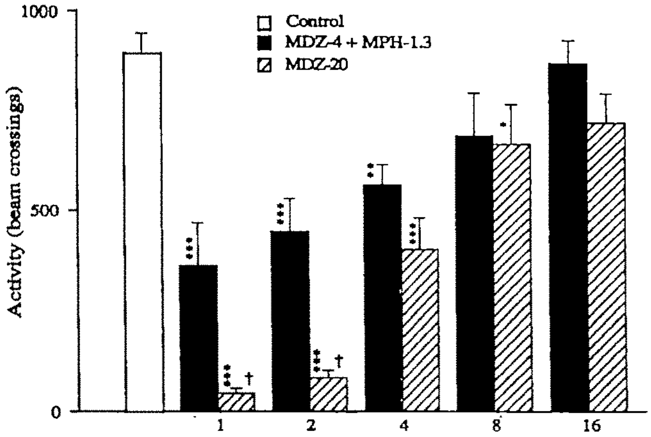

Figure 1. Effect of midazolam (MDZ) and midazolam-morphine (MPH) combination in equipotent hypnotic doses (MDZ 20 mg/kg and MDZ 4 mg/kg + MPH 1.3 mg/kg) on the locomotor activity in rats after recovery of the righting reflex. *Vertical axis*, number of beam crossings for 15 min; *horizontal axis*, time from injection. $^{*}P < 0.05$ versus control; $^{**}P < 0.005$ versus control, $^{***}P < 0.001$ versus control; $^{\dagger}P < 0.005$ versus MDZ + MPH.

Results

The duration of loss of the righting reflex in the midazolam and midazolam-morphine groups was 30 ± 3 and 28 ± 2 min, respectively; that indirectly confirmed the hypnotic equipotency of the chosen doses. The changes in the locomotor activity of the animals after recovery from hypnosis are presented in Figure 1. Figure 1 demonstrates a pronounced difference in the locomotor activity between midazolam and midazolam-morphine in the 1- and 2-h subgroups (46 ± 13 vs 360 ± 109 crossings, $P < 0.005$; 85 ± 18 vs 447 ± 84 crossings, $P < 0.005$, respectively). Although there were numerical differences between the two groups after 2 h, they were statistically insignificant.

Discussions

The results obtained in the present study demonstrated that despite equal duration of loss of the righting reflex caused by equipotent (for hypnotic effect) doses of midazolam and the midazolam-morphine combination, locomotor activity in rats after recovery from hypnosis is depressed more when midazolam is used alone. The difference in locomotor activity for the two treatments is very profound.

Inhibition of locomotor activity in animals is commonly regarded as an index for sedative action (6). The present study gave the opportunity to test two actions, hypnotic and sedative, in the same experiment when one of them was followed by another. As a result, it was possible to demonstrate the abrupt disappearance of the synergy between midazolam and morphine and the long-lasting difference in the sedative effect of the two treatments given in the doses equipotent for hypnotic effect. Differences in the outcomes of the midazolam-morphine interaction with regard to sedation and hypnosis suggest that these two actions should not be regarded as only increasing depths of the same action.

We suggest that the additive midazolam-morphine interaction for sedation is mainly due to the pharmacodynamic mechanisms. Previously reported results (2) with brain concentration-related analysis of the morphine-diazepam hypnotic interaction demonstrated the same degree of synergism as results with dose-related analysis of the same interaction. This outcome decreases the probability that pharmacokinetic factors play a significant role in the morphine-benzodiazepine hypnotic synergism. At the same time, differences in the pharmacokinetic interactions for relatively high concentrations (providing hypnosis) and for lower concentrations of agents (providing sedation), although unlikely, are possible. Therefore, pharmacokinetic aspects of the midazolam-morphine sedative interaction deserve further elucidation. As for the less pronounced depression of locomotor activity following hypnosis with the midazolam-morphine combination versus midazolam alone, it is most likely due to considerably smaller concentrations of midazolam at the target sites at a time when the synergism between midazolam and morphine is lost after recovery from hypnosis.

The clinical implication of these results is that a benzodiazepine-opioid combination in hypnotic doses that are equipotent to a benzodiazepine alone might result in less sedation after awakening. Previously reported results confirmed a profound benzodiazepine-opioid hypnotic synergism in patients (1,7). At the same time, when a midazolam-morphine combination was studied in patients with regard to its sedative effect, only simple summation of the effects was found (8). This difference indicates that the results reported in the present study might be very indicative of what to expect in patients.

In conclusion, the results of the present study confirmed the hypothesis that sedation after recovery from midazolam-induced hypnosis is more profound than sedation after hypnosis induced by mi
morphine combination.

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Intramuscularly Administered Dexmedetomidine Attenuates Hemodynamic and Stress Hormone Responses to Gynecologic Laparoscopy

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The hemodynamic and endocrine effects of three different doses of dexmedetomidine (0.6, 1.2, and 2.4 μg/kg), oxycodone (0.13 mg/kg), and saline solution, injected intramuscularly 45–60 min before induction of general anesthesia, were compared in a double-blind, randomized study involving 100 women undergoing gynecologic diagnostic laparoscopy. Anesthesia was induced with thiopental (4.5 mg/kg) and maintained with 0.3% end-tidal isoflurane and 70% nitrous oxide in oxygen. Arterial blood pressure and heart rate increased after endotracheal intubation and during laparoscopy in all groups, but the maximal mean arterial pressure after tracheal intubation was lower in the dexmedetomidine 2.4-μg/kg group (104 mm Hg [SD 19]) than in the saline solution group (130 mm Hg [SD 12]). Dexmedetomidine (2.4 and 1.2 μg/kg) attenuated the maximal heart rate after intubation (84 [SD 11] and 101 beats/min [SD 15], respectively) compared with saline solution (116 beats/min [SD 19]). On the other hand, 40% of the patients in the dexmedetomidine 2.4-μg/kg group received atropine in the postanesthesia care unit for bradycardia (heart rate $\leq$40 beats/min). Preoperative anxiety and sedation before and after preanesthetic medication were evaluated by the patients with the aid of a profile of mood-state questionnaire; only dexmedetomidine 2.4 μg/kg produced significant anxiolysis and sedation. Plasma concentrations of norepinephrine, epinephrine, 3,4-dihydroxyphenylglycol, cortisol, and β-endorphin increased less in the dexmedetomidine 2.4-μg/kg group in response to tracheal intubation and surgery than in the saline solution group.

(Anesth Analg 1992;75:932–9)

Recent studies with α_2-adrenoceptor agonists have demonstrated beneficial effects in anesthetized patients (1–3). Clonidine attenuates hemodynamic responses during laryngoscopy and endotracheal intubation (2,3). It also reduces dose requirements of inhaled anesthetics (4–8) during surgical stimulation. In addition, α_2-adrenoceptor agonists may have clinically significant anxiolytic activity (9).

Dexmedetomidine is a highly specific, potent, and selective α_2-adrenoceptor agonist (10,11). Racemic medetomidine is widely used as a sedative and an anesthetic in domestic animals (12). In humans, dexmedetomidine, the active dextroisomer that exhibits sedative properties, is well tolerated (13,14). Subjective sleepiness appears within 5 min after intravenous administration and reaches its maximum 15 min after the drug injection (14). Dexmedetomidine caused a dose-dependent decrease in arterial blood pressure and heart rate (HR) (13), and reduction in sympathetic nervous activity was manifested as a dose-dependent decline in plasma levels of norepinephrine (13,15). Single intravenous doses of dexmedetomidine administered 15 min before the induction of anesthesia decreased thiopental requirements during cervical dilatation and uterine curettage (16), attenuated the hemodynamic responses to laryngoscopy and endotracheal intubation, and diminished isoflurane requirements during abdominal hysterectomy (17).

Nociceptive surgical stimulation is accompanied by increased sympathoadrenal and hypothalamopituitary activation (18,19), which is generally referred to as the stress response to surgery (19–21). Plasma concentrations of cortisol, immunoreactive β-endorphin, and catecholamines increase in response to

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Table 1. Demographic Data of 99 Patients Undergoing Elective Diagnostic Gynecologic Laparoscopy

	Saline solution group (n = 20)	Oxycodone group (0.13 mg/kg; n = 20)	Dexmedetomidine groups	
			0.6 μg/kg (n = 19)	1.2 μg/kg (n = 20)
Age (yr)	32 (5)	30 (4)	31 (4)	31 (5)
Weight (kg)	60 (9)	62 (8)	68 (8)[a]	60 (8)
Height (cm)	165 (6)	166 (5)	169 (8)	164 (4)
MAP (mm Hg)	82 (10)	85 (10)	91 (11)[b]	84 (12)
HR (beats/min)	71 (17)	73 (14)	72 (12)	72 (11)

MAP, mean arterial blood pressure; HR, heart rate.
All values are mean (SD).
[a] Significantly different from saline solution and dexmedetomidine (1.2 and 2.4 μg/kg) groups.
[b] Significantly different from saline solution and dexmedetomidine (2.4 μg/kg) groups.

tracheal intubation (22,23) and surgery (24). Local anesthetic techniques (19) and anesthetic drugs modify the release of these stress hormones into the peripheral circulation during surgical stress.

In the present study, we investigated the effects of three different preanesthetic doses of intramuscularly injected dexmedetomidine on hemodynamics during isoflurane anesthesia in patients undergoing gynecologic laparoscopy. For comparison, similar groups of patients were injected intramuscularly with a synthetic narcotic analgesic, oxycodone, or saline solution. This route of administration was chosen because α_2-adrenergic drugs result in smoother hemodynamic response after intramuscular than intravenous administration (13). To gain more information from the simultaneous effect of dexmedetomidine on both the hypothalamopituitary and sympathoadrenal responses to stress during the procedure, we measured plasma concentrations of cortisol, β-endorphin, and catecholamines (norepinephrine, epinephrine, and 3,4-dihydroxyphenylglycol [DHPG]).

Methods

The study protocol was approved by the Ethical Committee of Women's Hospital, University of Helsinki. Written, informed consent was obtained from each patient. The study population comprised 100 women, aged 20–42 yr, undergoing elective diagnostic gynecologic laparoscopy. All were healthy, normotensive, ASA physical status I patients receiving no medication. Demographic characteristics are shown in Table 1.

The patients were randomized into five groups (n = 20 in each group). On the day of surgery, premedication was administered from coded ampules into the vastus lateralis muscle 45–60 min before induction of anesthesia. Patients received either dexmedetomidine hydrochloride (0.6, 1.2, or 2.4 μg/kg) (Orion Corporation Farmos, Turku, Fin-
land), oxycodone chloride (0.13 mg/kg) (
Leiras, Helsinki, Finland), or saline soluti
double-blind design was maintained by h
independent nurse prepare the drug solutio
in a volume of 1 mL. Before administratio
study drugs, electrocardiographic monitori
II) and automatic noninvasive arterial blood
measurements were instituted.

Before induction of anesthesia, the pati
ceived intravenous glycopyrrolate (0.2 n
vecuronium bromide (0.6 mg). Anesthesia v
induced with thiopental (4.5 mg/kg), and s
choline (1.5 mg/kg) was administered to
laryngoscopy and endotracheal intubation. A
sia was maintained with 0.3% end-tidal isofl
70% nitrous oxide and 30% oxygen. After t
nylcholine-induced neuromuscular blockade
sipated, vecuronium bromide was titrated to
and maintain 80% relaxation, as assessed
nerve stimulator (25). Laparoscopy began n
than 15 min after tracheal intubation and
formed with the table at a 15° head-down
ensure adequate visibility in the surgical f
peritoneal cavity was filled with carbon dio
pressure of 10–12 mm Hg. No opioids were
tered during the procedure. Isoflurane ad
tion was terminated immediately after the re
the laparoscope, and at the end of anesthe
romuscular blockade was reversed with neo
(2 mg) and glycopyrrolate (0.4 mg). In the p
thesia care unit, intravenous fentanyl was
tered for moderate or severe pain in inc
doses of 0.05 mg.

Arterial blood pressure and HR were
with a noninvasive, automated blood pressu
itor (Datascope Accutor, Datascope Corp.
(baseline) and at 10-min intervals after pre
tion. The measurements were performed
intervals during induction, for the first 10 r
tracheal intubation, and thereafter at 2.5-m

vals throughout the duration of anesthesia. In the postanesthesia care unit, arterial blood pressure and HR were recorded at 15-min intervals. The electrocardiogram was monitored throughout the premedication period, during the laparoscopy, and in the postanesthesia care unit.

Sedation scores (1 = awake, eyes open; 2 = asleep, but arousable) were assessed by a research nurse before premedication and just before induction of anesthesia.

The patients were requested to fill out the Finnish version of the profile of mood-state (POMS) questionnaire, which consisted of seven adjectives related to fatigue and eight adjectives related to tension and anxiety, before administration of a study drug. The questionnaire was repeated immediately before induction of anesthesia. The Finnish version of POMS has previously been standardized in normal female populations (26) and used in the evaluation of premedication (26).

Need of fentanyl doses in the postanesthesia care unit was recorded.

Plasma cortisol was measured in all patients; plasma immunoreactive β-endorphin only in the patients who received either the largest dose of dexmedetomidine (2.4 μg/kg) or saline solution. Plasma concentrations of norepinephrine, epinephrine, and DHPG, a deaminated metabolite of norepinephrine, were measured in patients receiving dexmedetomidine (1.2 or 2.4 μg/kg), oxycodone, or saline solution. Before premedication, control baseline blood samples for plasma cortisol, immunoreactive β-endorphin, DHPG, epinephrine, and norepinephrine determinations were drawn from an intravenous antecubital cannula. Blood samples were collected again just before induction of anesthesia, 5 and 15 min after tracheal intubation, 10 min after the beginning of laparoscopy, and 1 h after the procedure. Blood samples were collected into prechilled K_2-ethylenediaminetetraacetate tubes and promptly centrifuged. Plasma was separated and stored at −70°C. Cortisol analyses were carried out by radioimmunoassay (27), having an intraassay coefficient of variation of 3%, using commercially available reagents (Orion Corporation Farmos). Radioimmunoassays of immunoreactive β-endorphin were performed after extraction of the plasma samples using SEP PAK C18 cartridges (Water Associates Inc., Milford, Mass.), as described previously by Laatikainen et al. (28). The intraassay coefficient of variation for the determination of immunoreactive β-endorphin was 11%. Levels of endogenous catecholamines were determined using high-performance liquid chromatography with electrochemical detection (29). The intraassay coefficients of variation were <2% for norepinephrine, 4% for DHPG, and 10% for epinephrine.

Statistical analyses were performed using two-way analysis of covariance (ANCOVA) for repeated measures to determine whether differences in the response (arterial blood pressure, HR, hormone concentration) varied significantly over time between the study drugs (drug by time interaction) and whether the mean levels of response for the study drugs differed significantly (drug main effect). When a statistically significant drug by time interaction or drug effect was present, the analysis was continued by applying contrasts for each pair of different drugs with Bonferroni correction. For demographic data and single endpoints (e.g., maximal HR and arterial blood pressure), one-way analysis of variance or ANCOVA was used with Bonferroni-corrected *t*-tests for pairwise comparisons. The POMS tension-anxiety and fatigue scores and the nurse's sedation scores were analyzed with nonparametric Kruskal-Wallis one-way analysis of variance using Bonferroni-corrected Mann-Whitney tests for pairwise comparisons. A *P*-value <0.05 was considered statistically significant. The analyses were performed with BMDP software.

Results

The five groups were comparable with respect to age, height, baseline HR, duration of surgery (18 min [SD 9]), and intraoperative fluid requirements (Table 1). The patients in the dexmedetomidine 0.6-μg/kg group were heavier and had higher mean arterial blood pressure (MAP) than most of the other patients. One of the patients enrolled in this group was withdrawn because laparoscopy was followed by laparotomy during the same anesthesia.

There were no statistically significant differences in the need for analgesic medication in the postanesthesia care unit: 90% of patients in the saline solution group, 79% in the dexmedetomidine 0.6-μg/kg group, 85% in the dexmedetomidine 1.2-μg/kg group, 65% in the dexmedetomidine 2.4-μg/kg group, and 60% in the oxycodone group received fentanyl.

Sedation and Anxiolysis

The sedative effect of the largest dose of dexmedetomidine (2.4 μg/kg), as assessed by the research nurse 45–60 min after preanesthetic medication, was significant compared with the saline solution group ($P = 0.02$; Mann-Whitney test) but was not significantly different from that of the lower doses of dexmedetomidine or oxycodone (Table 2).

The POMS tension-anxiety scores decreased in all patient groups after preanesthetic medication, but the decrease was most significant in the dexmedetomidine 2.4-μg/kg group (Table 2). The POMS fatigue

Table 2. Number of Sedated Patients Just Before Induction of Anesthesia and Changes in POMS Tension-Anxiety and Fatigue Scores Before and After Preanesthetic Medication

	Saline solution group (n = 20)	Oxycodone group (0.13 mg/kg; n = 20)	Dexmedetomidine groups		
			0.6 μg/kg (n = 19)	1.2 μg/kg (n = 20)	2.4 μg/kg (n = 20)
Sedated pts	2	5	5	4	11^{a}
ΔT-A scores	0.25 (0.22)	0.50 (0.56)	0.25 (0.34)	0.44 (0.36)	0.50 (0.34)^{a}
ΔFatigue scores	−0 (0.27)	−0.43 (0.43)	−0.14 (0.36)	−0.07 (0.34)	−0.79 (0.46)^{b,c}

Sedated pts, patients (pts) lying with eyes closed, but arousable; T-A, tension-anxiety; POMS, profile of mood-state questionnaire.
Values are POMS scores, median (quartile deviation) differences between before and after medication scores.
[a] $P < 0.05$ vs saline solution group.
[b] $P < 0.01$ vs saline solution group.
[c] $P < 0.05$ vs dexmedetomidine (0.6 and 1.2 μg/kg) groups.

Table 3. Mean Arterial Pressure and Heart Rate Before, During, and After Anesthesia in Patients Undergoing Gynecologic Laparoscopy

	Saline solution group	Oxycodone group (0.13 mg/kg)	Dexmedetomidine groups		
			0.6 μg/kg	1.2 μg/kg	2.4 μg/kg
MAP (mm Hg)					
Baseline	82 (10)	85 (10)	91 (11)^{a}	84 (12)	80 (9)
Min before induction	75 (9)	78 (7)	78 (8)	70 (10)^{b,c}	64 (8)^{d,e}
At induction	90 (10)	93 (12)	93 (11)	82 (17)^{a,f}	76 (14)^{b,c}
Max after intubation	130 (12)	120 (17)	133 (16)	121 (19)	104 (19)^{d}
Max during scopy	114 (18)	113 (16)	116 (15)	105 (12)	101 (19)
Mean during scopy	99 (5)	100 (14)	103 (11)	93 (11)	87 (18)^{a,f}
Min in PACU	66 (9)	67 (10)	67 (9)	62 (10)	59 (9)^{f}
1 h in PACU	74 (9)	76 (7)	73 (10)	68 (12)	68 (15)
HR (beats/min)					
Baseline	71 (17)	73 (14)	72 (12)	72 (11)	65 (10)
Min before induction	65 (10)	64 (9)	65 (11)	64 (10)	53 (7)^{c,d}
At induction	76 (16)	75 (13)	76 (12)	74 (11)	60 (10)^{b,f}
Max after intubation	116 (19)	106 (15)	108 (13)	101 (15)^{b}	84 (11)^{c,d}
Max during scopy	112 (12)	100 (13)^{a}	106 (12)	97 (13)^{b}	83 (9)^{b,e}
Mean during scopy	96 (14)	88 (10)	93 (8)	85 (11)^{a}	72 (10)^{d,e}
Min in PACU	55 (6)	57 (5)	52 (6)	52 (7)	45 (7)^{d,e}
1 h in PACU	62 (10)	63 (5)	59 (10)	58 (10)	53 (8)^{b,c}

MAP, mean arterial pressure; Min before induction, lowest value measured after preanesthetic medication but before induction of anesthesia; Max after intubation, highest value measured 1–5 min after intubation; Max during scopy, highest value measured during laparoscopy; Min in PACU, lowest value measured during 2 h in postanesthesia care unit; 1 h in PACU, value measured 1 h after the end of laparoscopy; HR, heart rate.
All values are mean (SD). Only pairwise comparison with saline and oxycodone are pointed out.
[a] $P < 0.05$ vs saline.
[b] $P < 0.01$ vs saline.
[c] $P < 0.01$ vs oxycodone.
[d] $P < 0.001$ vs saline.
[e] $P < 0.001$ vs oxycodone.
[f] $P < 0.05$ vs oxycodone.

scores increased significantly more after dexmedetomidine 2.4 μg/kg than after saline solution or dexmedetomidine 0.6 or 1.2 μg/kg (Table 2).

Arterial Blood Pressure

The MAP followed similar patterns in all groups (Table 3). After administration of the preanesthetic study drugs, MAP values before induction differed among the groups. Dexmedetomidine caused a significant, dose-dependent decrease in MAP before anesthesia, whereas oxycodone did not. The MAP increased after endotracheal intubation in all groups, but dexmedetomidine attenuated this response in a dose-dependent manner. The highest MAP values observed after intubation in the dexmedetomidine 2.4-μg/kg group (104 mm Hg [SD 19]) were significantly lower ($P < 0.001$; t-test) than in the saline solution group (130 mm Hg [SD 12]), with a 95% confidence interval from −39 to −10 mm Hg for the difference between the two groups. During laparoscopy, MAP increased again in all groups, but there was a significant difference in maximal MAP among them ($P = 0.02$; ANCOVA). The maximal MAP was lowest in the dexmedetomidine 2.4-μg/kg group. In the postanesthesia care unit MAP values were also lowest in patients premedicated with dexmedetomidine 2.4 μg/kg.

Heart Rate

Before induction, dexmedetomidine 2.4 μg/kg decreased HR significantly compared with both saline solution ($P < 0.001$) and oxycodone ($P = 0.02$) (Table 3). The HR increased in all groups after intubation, but the increase was less in the dexmedetomidine 2.4-μg/kg group compared with the oxycodone and saline solution groups, with a 95% confidence interval from −42 to −16 beats/min for the difference versus the saline solution group. Dexmedetomidine 1.2 μg/kg blunted the HR increase significantly compared with the saline solution group. The HR increased in all groups during laparoscopy. The maximal values were significantly greater in the saline solution group compared with the oxycodone ($P = 0.02$) and dexmedetomidine 1.2-μg/kg ($P = 0.001$) and 2.4-μg/kg ($P < 0.001$; *t*-test) groups.

In the postanesthesia care unit, patients premedicated with dexmedetomidine 2.4 μg/kg had lower HR than the others (Table 3). Eight of the 20 patients in this group had HR transiently <40 beats/min and were treated with atropine (0.4 mg). In contrast, there were no atropine-treated patients in the other groups. No electrocardiographic changes other than sinus bradycardia were observed, and the response to atropine was adequate.

Stress Hormones in Plasma

Plasma cortisol concentrations were lowest before induction of anesthesia in the patients premedicated with dexmedetomidine 2.4 μg/kg or with oxycodone. After intubation or during laparoscopy, increases were observed in all groups; in the saline solution group, maximal levels had already been reached after intubation. The cortisol values remained lowest after intubation in the oxycodone and dexmedetomidine 2.4-μg/kg groups (Figure 1). The cortisol concentrations increased postoperatively to similar levels in all groups.

Before induction, there was no difference in plasma immunoreactive β-endorphin between the highest dose of dexmedetomidine and saline solution. In the saline solution group, plasma β-endorphin increased significantly more in response to laryngoscopy and laparoscopy compared with the dexmedetomidine 2.4-μg/kg group (Figure 2).

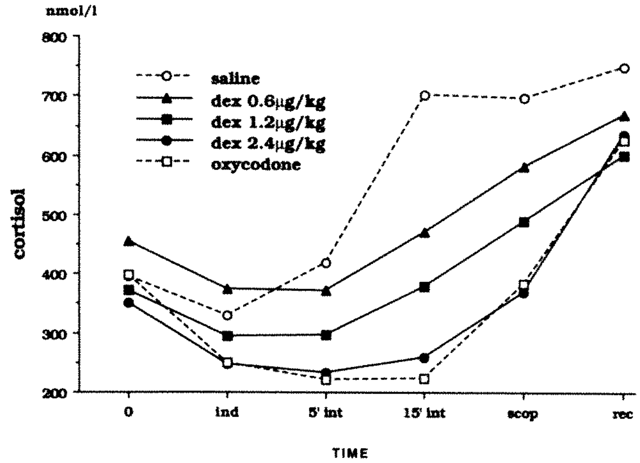

Figure 1. Mean cortisol concentrations in peripheral plasma just before preanesthetic medication (O), just before induction (ind) of anesthesia, 5 and 15 min after intubation ('int), 10 min after beginning of laparoscopy (scop), and 1 hour after operation in the postanesthesia care unit (rec). Standard deviations have been omitted for clarity. *Key to abbreviations*: a = dexmedetomidine (dex) 2.4 μg/kg versus saline solution; b = oxycodone versus saline solution; c = dexmedetomidine 2.4 μg/kg versus oxycodone. Drug main effect: $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$. Drug by time interaction: #$P < 0.05$, ##$P < 0.01$, ###$P < 0.001$, NS = not significant. In this figure: a = ***, ###; b = ***, ###; c = NS, NS.

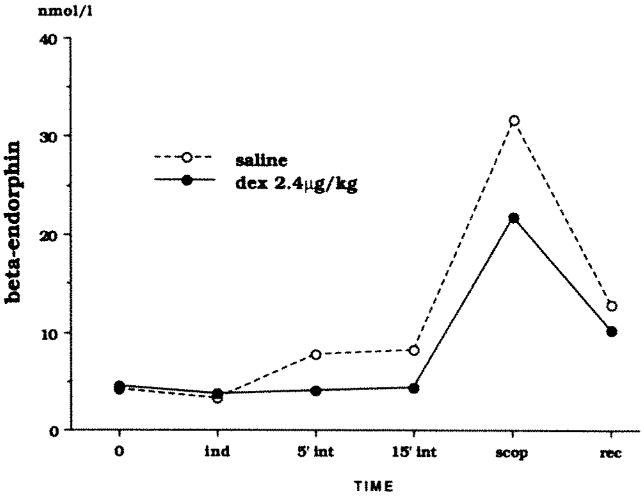

Figure 2. Mean β-endorphin concentrations in peripheral plasma. Standard deviations have been omitted for clarity. In this figure a = *, NS. See Figure 1 for explanation of abbreviations.

Dexmedetomidine induced approximately 70% reductions in plasma norepinephrine concentrations. Both dexmedetomidine 1.2- and 2.4-μg/kg groups differed from saline solution and oxycodone groups (Figure 3). The highest norepinephrine values were observed postoperatively in the saline solution group.

Plasma DHPG was reduced by approximately 20%

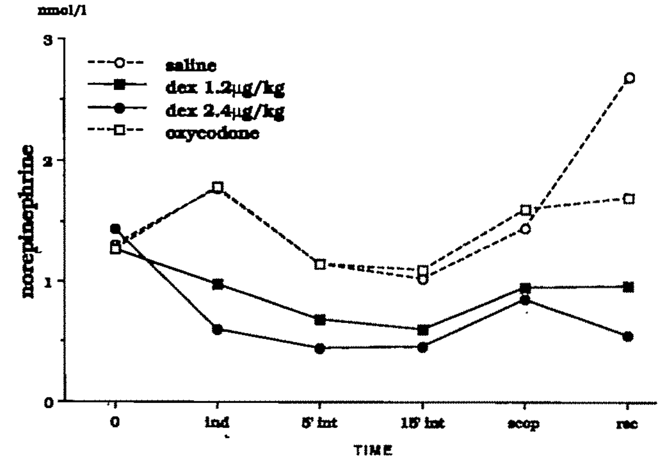

Figure 3. Mean norepinephrine concentrations in peripheral plasma. Standard deviations have been omitted for clarity. In this figure: a = ***, ###; b = NS, NS; c = ***, ###. See Figure 1 for explanation of abbreviations.

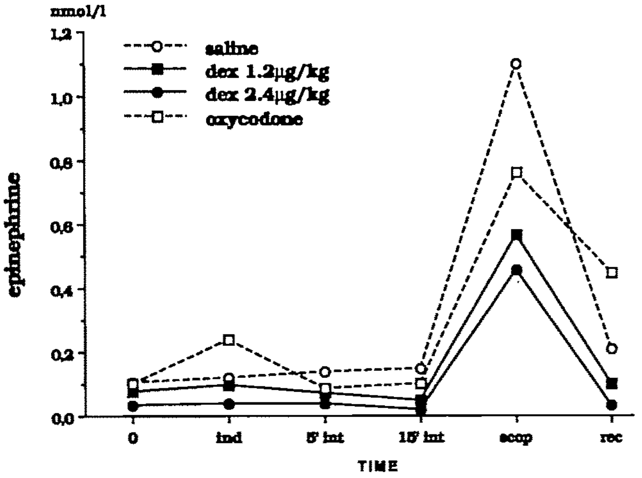

Figure 5. Mean epinephrine concentrations in peripheral plasma. Standard deviations have been omitted for clarity. In this figure: a = ***, NS; b = NS, NS; c = NS, ##. See Figure 1 for explanation of abbreviations.

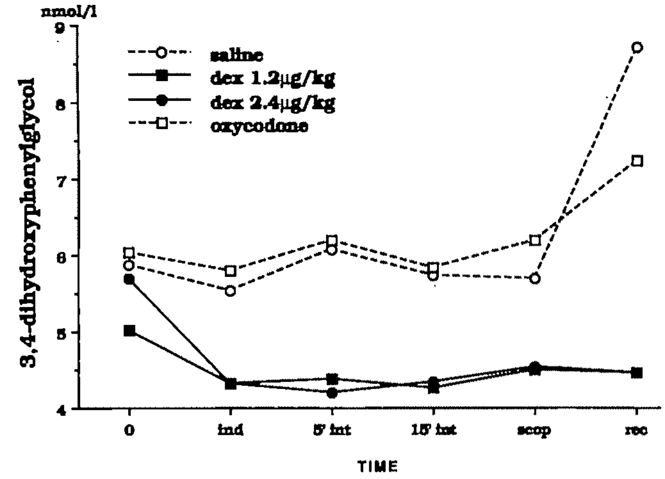

Figure 4. Mean 3,4-dihydroxyphenylglycol concentrations in peripheral plasma. Standard deviations have been omitted for clarity. In this figure: a = NS, #; b = NS, NS: c = ***, NS. See Figure 1 for explanation of abbreviations.

in the dexmedetomidine 2.4-µg/kg group immediately after administration of preanesthetic medication. In the saline solution and oxycodone groups, the values remained at the baseline level. This difference was maintained throughout the study period. There was a marked increase in DHPG values postoperatively in the saline solution and oxycodone groups, which contrasted with the stable values in the dexmedetomidine groups (Figure 4).

The plasma epinephrine concentrations increased markedly during laparoscopy in all groups. The increase was smaller in the dexmedetomidine groups compared with the oxycodone and saline solution groups. This difference in epinephrine concentrations was maintained in the postanesthesia care unit (Figure 5).

Discussion

The most important findings in this investigation were related to changes in HR and arterial blood pressure. During the preanesthetic period, the highest dose of dexmedetomidine (2.4 µg/kg) caused a significant reduction in MAP but without provoking any subjective symptoms. Laryngoscopy, endotracheal intubation, and gynecologic laparoscopy induced significant increases in arterial blood pressure in all study groups, but to a lesser extent after dexmedetomidine 2.4 µg/kg than after the other drugs. Dexmedetomidine reduces HR (13), and this was dose-dependently observed in our study at doses of 1.2 and 2.4 µg/kg. The increase in HR in response to intubation and laparoscopy was substantially blunted by dexmedetomidine. This might be beneficial in patients at risk for myocardial ischemia secondary to tachycardia (30). In the postanesthesia care unit, atropine was administered to treat sinus bradycardia (i.e., HR <40 beats/min) in 8 of the 20 patients in the highest-dose dexmedetomidine group and in none in the other groups. Although this indicates that the effect of dexmedetomidine was still apparent during the recovery period, the premedication did not alter the need for analgesics. Bradycardia and a concomitant slight decrease in MAP may be clinically unimportant in ASA physical status I patients but may restrict the use of this drug in patients prone to bradycardia, as has been pointed out concerning another α_2-adrenergic agonist, clonidine (1).

Our findings with regard to surgery-related stress responses are in agreement with several studies on the effects of the prototype α_2-adrenergic agonist clonidine. Oral clonidine (4.5 μg/kg) attenuated the sympathoadrenal response to tracheal intubation in patients undergoing breast surgery under general anesthesia (31). The plasma norepinephrine levels were lower throughout the procedure, and the plasma epinephrine concentrations were lower after intubation in the clonidine-pretreated patients compared with the control group (31). In our previous study, we administered clonidine (3 and 4.5 μg/kg IM) and demonstrated that the increases in arterial blood pressure and HR in response to endotracheal intubation and laparoscopy were attenuated in the clonidine-pretreated patients (32). The α_2-adrenergic agonists exert their sympatholytic effect presumably by activating inhibitory α_2-adrenergic receptors, both in the central nervous system and on peripheral sympathetic nerve endings (presynaptic autoreceptors) (33–35). This action leads to inhibition of release of norepinephrine from sympathetic nerve endings (35,36). The inhibition of sympathetic transmitter release can be measured in humans as a decrease in the concentration of norepinephrine in plasma (13, 15,29,31).

In the present study, dexmedetomidine induced marked and sustained reductions in plasma concentrations of norepinephrine and its deaminated metabolite DHPG. The initial DHPG decrease is in line with our previous observations (29), but the total attenuation of the DHPG increase during surgery by dexmedetomidine appears to be a new finding. It indicates that plasma DHPG measurements may be useful in the evaluation of the sympathoinhibitory effects of preanesthetic medications. Suppression of epinephrine release was not complete during and after laparoscopy, but a difference was observed when the two highest doses of dexmedetomidine (1.2 and 2.4 μg/kg) were compared with either saline solution or oxycodone. When lower doses of dexmedetomidine were administered intramuscularly before minor surgery, similar dose-dependent reductions in norepinephrine concentrations were observed (37).

The attenuation of cortisol and β-endorphin responses to surgical stimulation reflects inhibition of stress responses, comparable to the effects of opioids (24) or deeper levels of general anesthesia (21,22). In our previous study, clonidine 4.5 μg/kg attenuated the β-endorphin response to laparoscopy (32). However, controversial results have been obtained in studies on the noradrenergic control of cortisol release. The α_2-adrenoceptor agonists did not directly influence cortisol secretion under basal conditions (13,38), and oral clonidine premedication did not suppress the release of cortisol in response to anesthesia and surgery (31). Similarly, in a recent study with intravenous dexmedetomidine, plasma cortisol levels were not affected, and a relatively small dose of dexmedetomidine did not inhibit the increase in plasma cortisol concentrations after minor surgery (39). In the present study, the concentration of cortisol in plasma decreased in a dose-dependent fashion. The effect of the highest dose of dexmedetomidine (2.4 μg/kg) was comparable to the effect of oxycodone, although marked postoperative increases in plasma cortisol were observed in all groups. One explanation for our finding, which has not been reported previously, is that we used a large dose of dexmedetomidine before a moderately stressful procedure carried out under relatively light anesthesia.

Dexmedetomidine (2.4 μg/kg) injected intramuscularly produced both sedation and a reduction in anxiety, as measured with POMS; yet patients were responsive and free from subjective side effects. Anxiolytic and sedative effects of dexmedetomidine were comparable to those seen with benzodiazepines (26).

In conclusion, intramuscularly administered dexmedetomidine resulted in sedation and anxiolysis and blunted the hemodynamic and hormonal responses to noxious stimuli during laparoscopy. Sinus bradycardia may be associated with dexmedetomidine premedication, although it was asymptomatic and readily reversed by atropine in our patients.

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Dexmedetomidine Infusion for Maintenance of Anesthesia in Patients Undergoing Abdominal Hysterectomy

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The usefulness of intravenous dexmedetomidine infusion for maintenance of anesthesia was studied in patients anesthetized with thiopental, fentanyl, nitrous oxide, and oxygen. Isoflurane was added as needed. The study was conducted in two parts, the first of which was an open dose-response study that comprised 14 women undergoing abdominal hysterectomy. After a suitable infusion regimen of dexmedetomidine was determined according to hemodynamic criteria, 20 patients were included in a double-blind, randomized placebo-controlled trial (10 receiving dexmedetomidine, 10 saline solution). Dexmedetomidine was administered as a two-step infusion to rapidly achieve a steady-state plasma concentration. The infusion was started with an initial dose given over 10 min before the induction of anesthesia; at induction the maintenance rate was begun and continued until closure of the abdominal fascia. The infusion regimens of dexmedetomidine tested in the dose-response study ranged from 120 $ng \cdot kg^{-1} \cdot min^{-1}$, followed by 6 $ng \cdot kg^{-1} \cdot min^{-1}$, to 270 + 13.5 $ng \cdot kg^{-1} \cdot min^{-1}$. In the second part of the study, an initial infusion of 170 $ng \cdot kg^{-1} \cdot min^{-1}$ was chosen, followed by 10 $ng \cdot kg^{-1} \cdot min^{-1}$ for maintenance. Anesthesia was induced with thiopental (4.0 mg/kg) and maintained with isoflurane in 70% nitrous oxide and oxygen. Isoflurane was administered according to predetermined hemodynamic criteria. Dexmedetomidine infusion did not completely abolish the need for isoflurane but diminished its requirement by >90% (P = 0.02). The heart rate response to endotracheal intubation was significantly blunted.

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The α_2-adrenergic agonists produce sedation (1) and reduce anesthetic requirements in several animal models (2–5). The prototype α_2-adrenergic agonist, clonidine, has been used for its hemodynamic stabilizing effect (6–8) and for its anesthetic-sparing effect during cardiopulmonary bypass (9), during vascular surgery (10), and in elderly patients (11). Postoperative clonidine infusion reduces heart rate and plasma norepinephrine, epinephrine, and vasopressin concentrations (12).

Dexmedetomidine, an imidazole derivative, is a selective and full α_2-adrenoceptor agonist possessing sedative properties (13–15). It is well tolerated but causes a dose-dependent decrease in arterial blood pressure and heart rate (HR) associated with a decrease in plasma norepinephrine concentrations (14). Sleepiness appears within 5 min after intravenous administration of dexmedetomidine and reaches its maximum within 15 min (16). A single intravenous bolus dose of dexmedetomidine administered 15 min before induction of anesthesia diminished thiopental requirement during cervical dilatation and uterine curettage procedures (17). Dexmedetomidine administered by a single intravenous injection attenuates hemodynamic responses to laryngoscopy and endotracheal intubation and decreases isoflurane requirement for anesthetic maintenance by 30% (18).

In this study, we evaluated the effects of a continuous, two-step intravenous infusion of dexmedetomidine on hemodynamic responses to laryngoscopy and endotracheal intubation and its usefulness during maintenance of anesthesia in patients undergoing abdominal hysterectomy.

Methods

The study protocol was approved by the Ethical Committee of Women's Hospital, University of Helsinki. Written, informed consent was obtained from each patient. The study was conducted in two parts.

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The first was an open dose-response study and comprised 14 women undergoing elective abdominal hysterectomy. The second part, accomplished after the suitable infusion regimen of dexmedetomidine had been determined, consisted of a double-blind, randomized, placebo-controlled trial involving 20 patients. All were healthy, normotensive, ASA physical status I or II women.

On the evening before surgery, patients received oral triazolam (0.125 mg). On the day of surgery, they received oral diazepam (0.2 mg/kg) 45–60 min before induction of anesthesia.

On arrival in the operating room, all patients had an intraarterial cannula inserted for arterial blood pressure monitoring and electrodes applied for continuous electrocardiographic monitoring. They were given glycopyrrolate (0.2 mg IV). The study drug was administered as a two-step intravenous infusion, starting at the higher (initial) rate for 10 min just before induction of general anesthesia. At induction, the lower (maintenance) rate was begun and continued until closure of the abdominal fascia. Just before induction, vecuronium (0.6 mg IV) and fentanyl (1.0 μg/kg IV) were administered. Anesthesia was induced with thiopental (4 mg/kg), and succinylcholine (1.5 mg/kg) was administered to facilitate laryngoscopy and endotracheal intubation. Anesthesia was maintained with dexmedetomidine infusion and inhalation of 70% nitrous oxide in oxygen. A second dose of fentanyl (1.0 μg/kg IV) was administered to all patients 2 min before surgical incision. Isoflurane was given, as needed, using the lowest possible end-tidal concentration necessary to maintain mean arterial blood pressure (MAP) within −30% to +15% and HR within −40% to +20% limits of the patient's preoperative baseline values. However, because of the chronotropic effect of glycopyrrolate, HR values were not taken into account until 30 min after the administration of glycopyrrolate. When isoflurane was required, its administration was started at 0.5% end-tidal concentration, and the concentration was increased by 0.2% increments at 2-min intervals until the hemodynamic variables returned to acceptable limits. Isoflurane concentration was also increased if any clinical signs of light anesthesia (e.g., bucking, swallowing, lacrimation, sweating, or movement) were observed. After the hemodynamic values had been maintained within acceptable limits for 4 min, the concentration of isoflurane was reduced by 0.2% decrements. Atropine (0.4 mg) was administered if HR decreased to below 40 beats/min. After the effect of succinylcholine had dissipated, vecuronium bromide (3 mg IV) was administered, with additional 1-mg doses to achieve and maintain 80% relaxation, as assessed with a neuromuscular monitor.

Nitrous oxide was discontinued at skin closure, and neuromuscular blockade was reversed with 2.0 mg of neostigmine, preceded by 0.4 mg of glycopyrrolate. In the postanesthesia care unit, oxycodone was administered intravenously in 0.06-mg/kg increments for postoperative pain relief.

The first part of the study was an open dose-response trial. Dexmedetomidine, diluted in normal saline solution to a concentration of 10 μg/mL, was administered by a continuous, two-step infusion. Infusion rates had been calculated according to the methods previously described by Wagner (19) and were based on pharmacokinetic variables reported by the manufacturer (elimination half-life 2.3 h; plasma clearance 12 $\mathrm{mL \cdot kg^{-1} \cdot min^{-1}}$). The first regimen tested consisted of a 120-$\mathrm{ng \cdot kg^{-1} \cdot min^{-1}}$ loading infusion, administered over 10 min, followed by a 6-$\mathrm{ng \cdot kg^{-1} \cdot min^{-1}}$ maintenance infusion, which was predicted to result in a 0.5-ng/mL steady-state plasma concentration of dexmedetomidine. In subsequent groups of patients, the initial rate was 170, 220, or 270 $\mathrm{ng \cdot kg^{-1} \cdot min^{-1}}$, respectively. The corresponding maintenance rates were 8.5, 11, and 13.5 $\mathrm{ng \cdot kg^{-1} \cdot min^{-1}}$, respectively. The predicted steady-state plasma concentrations of dexmedetomidine were 0.7, 0.9, and 1.1 ng/mL.

Because the classic arterial blood pressure response to a rapid intravenous administration of α_2-adrenoceptor agonists is biphasic (an initial increase followed by a longer lasting decrease [20]), the following hemodynamic cutoff rules for the infusion were used: (a) an increase in MAP >30% (excluding intubation); (b) systolic blood pressure >200 mm Hg or diastolic blood pressure >120 mm Hg; (c) a decrease in MAP of >40% or a MAP <50 mm Hg; and (d) HR <40 beats/min or an arrhythmia other than sinus bradycardia.

For the comparative part of the study, in which 10 patients received a dexmedetomidine infusion and 10 a saline solution infusion in a random, double-blind fashion, the optimal dexmedetomidine infusion rate was chosen such that it would not cause major hemodynamic responses during the initial infusion, but would reduce isoflurane requirements during surgery. A 170-$\mathrm{ng \cdot kg^{-1} \cdot min^{-1}}$ dexmedetomidine initial infusion rate and a 10-$\mathrm{ng \cdot kg^{-1} \cdot min^{-1}}$ maintenance rate was selected (see Results).

Intraarterial blood pressure and HR were continuously recorded throughout the study until the end of the operation. Preoperative baseline HR and arterial blood pressure values were determined in the operating room after a 5-min stabilization period. Postoperative arterial blood pressure and HR were determined with a noninvasive blood pressure monitor at 15-min intervals.

End-tidal isoflurane concentration was continuously assessed in the expired gas using an anesthetic

Table 1. Mean Arterial Pressure and Heart Rate During Initial Infusion of Dexmedetomidine at Four Different Rates in the Dose-Response Study

Dexmedetomidine ($ng \cdot kg^{-1} \cdot min^{-1}$)	Baseline	2 Min	4 Min	6 Min	8 Min	Intubation
120 + 6 ($n = 3$)						
MAP (mm Hg)	110 (7)	109 (5)	110 (4)	111 (9)	117 (6)	125 (17)
HR (beats/min)	67 (18)	82 (24)	77 (22)	72 (22)	67 (19)	81 (18)
170 + 8.5 ($n = 6$)						
MAP (mm Hg)	106 (5)	113 (6)	113 (7)	113 (7)	112 (10)	126 (6)
HR (beats/min)	72 (5)	79 (8)	72 (7)	68 (6)	65 (6)	74 (4)
220 + 11 ($n = 3$)						
MAP (mm Hg)	110 (8)	113 (9)	120 (6)	127 (5)	129 (7)	138 (5)
HR (beats/min)	81 (14)	84 (14)	75 (10)	72 (6)	66 (8)	79 (11)
270 + 13.5 ($n = 2$)						
MAP (mm Hg)	116 (6)	119 (14)	124 (2)	131 (2)	131 (2)	141 (12)
HR (beats/min)	75 (15)	82 (21)	66 (11)	61 (6)	59 (8)	73 (12)

MAP, mean arterial pressure; HR, heart rate; Baseline, values before start of dexmedetomidine infusion; 2, 4, 6, 8 min, values after start of dexmedetomidine initial infusion; Intubation, highest value measured 1–3 min after intubation.

Values are mean (SD).

agent monitor. To determine the intraoperative isoflurane requirements, the area under the end-tidal isoflurane concentration versus time curve was integrated.

In the second part of the study, sedation was assessed at arrival in the operating room and at 5 min after the beginning of the study drug infusion. Sedation was scored as 1 = awake, eyes open; 2 = asleep, easy to arouse.

The time to awakening, as determined by the time interval between the termination of nitrous oxide administration and eye-opening on request, was assessed.

Arterial blood samples were collected into prechilled K_2-ethylenediaminetetraacetate tubes 10, 20, 40, 60, and 120 min after the beginning of the infusion. In the comparative study, samples were also obtained 10, 30, and 120 min after the end of the infusion. The samples were centrifuged, and plasma was separated and stored at −20°C until analyzed. The concentration of dexmedetomidine in plasma was determined by a gas chromatographic/mass spectrometric method (21).

The total amount of oxycodone required for postoperative analgesia was recorded.

Only descriptive statistics are presented for the first part of the study because of the small number of patients in each treatment group. In the comparative part of the study, the statistical analyses for demographic data and single-efficacy variables (maximal HR and arterial blood pressure values, amount of oxycodone, and isoflurane concentration) were performed using the Student's *t*-test or Mann-Whitney test. Analysis of covariance (ANCOVA) for repeated measures (RM) was used for arterial blood pressure and HR. Greenhouse-Geisser adjustment was applied in case of nonsphericity in the correlation matrix of the orthogonal components. A *P*-value <0.05 was considered statistically significant. The statistical analyses were performed with BMDP software.

Results

Dose-Response Study

Four different infusion regimens (initial + maintenance rates) of dexmedetomidine were studied: 120 + 6 $ng \cdot kg^{-1} \cdot min^{-1}$ ($n = 3$); 170 + 8.5 $ng \cdot kg^{-1} \cdot min^{-1}$ ($n = 6$); 220 + 11 $ng \cdot kg^{-1} \cdot min^{-1}$ ($n = 3$); and 270 + 13.5 $ng \cdot kg^{-1} \cdot min^{-1}$ ($n = 2$). The four groups of patients were comparable with regard to age, weight, duration of operation, and the amount of perioperative fluid received.

The MAP increased in a dose-dependent manner during the initial infusion (Table 1). The two patients receiving dexmedetomidine infusion at the highest rate of 270 $ng \cdot kg^{-1} \cdot min^{-1}$ reached the predetermined hemodynamic cutoff endpoints, an increase in MAP of >30%, at 9 and 10 min after the start of infusion (maximal MAPs observed were 146 and 168 mm Hg), and the initial infusion had to be terminated at the induction of anesthesia.

The HR tended to decline with increasing dexmedetomidine dose, the lowest values being observed at approximately 6–8 min of infusion. Postoperatively, only one patient in the 120 + 6-$ng \cdot kg^{-1} \cdot min^{-1}$ group had a HR transiently <40 beats/min and was treated with atropine.

There was a minimal isoflurane requirement in all patients receiving ≥170 + 8.5 $ng \cdot kg^{-1} \cdot min^{-1}$ of dexmedetomidine (Figure 1). For that reason, and

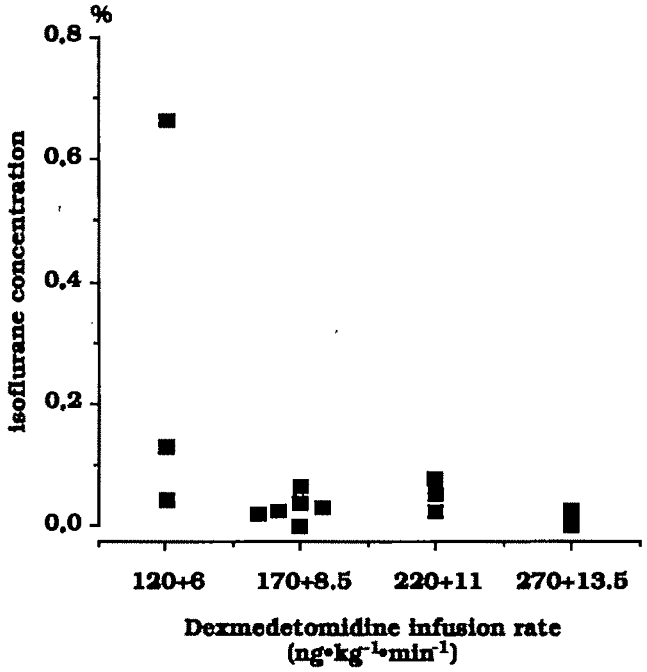

Figure 1. Isoflurane requirement of individual patients receiving different dexmedetomidine infusions (ng·kg^{-1}·min^{-1}): 120 + 6 (n = 3); 170 + 8.5 (n = 6); 220 + 11 (n = 3); 270 + 13.5 (n = 2). The mean isoflurane concentration was measured as the area under end-tidal concentration versus time curve.

because of better hemodynamic stability compared with higher doses, the 170-ng·kg^{-1}·min^{-1} initial infusion was selected for the double-blind study.

With this infusion rate, the plasma concentration of dexmedetomidine was 2.67 (SD 0.66) ng/mL at 10 min. Because subsequent drug plasma concentrations decreased slightly below the 0.7-ng/mL target concentration, in the second part of the study the maintenance infusion was increased to 10 ng·kg^{-1}·min^{-1}.

Comparative Study

The two patient groups were similar with respect to age, weight, height, duration of surgery, and total perioperative fluid administration. Demographic characteristics of the patients are shown in Table 2. There was no difference in the incidence of sedation 5 min after the beginning of the infusion: three patients in the dexmedetomidine group and one patient in the saline solution group were lying with their eyes closed. Likewise, there was no significant difference in the time to awakening (184 s [SD 122]) in the dexmedetomidine group versus the saline solution group (172 s [SD 153]).

Table 2. Clinical Characteristics of 20 Patients in the Comparative Study

	Saline solution group (n = 10)	Dexmedetomidine group (n = 10)
Age (yr)	43 (5)	42 (5)
Weight (kg)	66 (10)	63 (9)
Height (cm)	164 (6)	167 (5)
Duration of surgery (min)	107 (36)	112 (31)

Values are mean (SD).

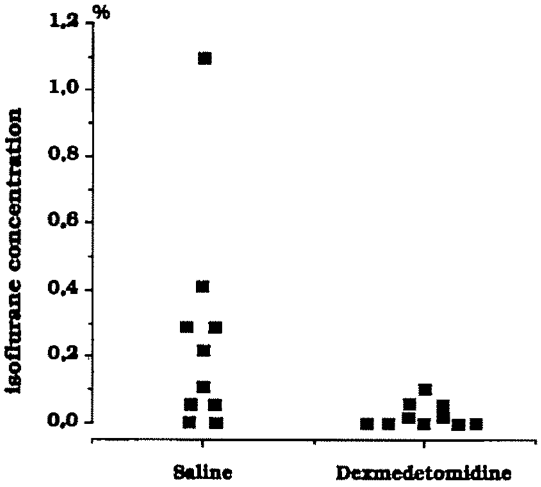

Figure 2. Isoflurane requirement of individual patients receiving normal saline solution or dexmedetomidine infusion (170 + 10 ng·kg^{-1}·min^{-1}). The mean isoflurane concentration was measured as the area under end-tidal concentration versus time curve.

Anesthetic Requirements

In the dexmedetomidine group, 5 of 10 patients did not require any isoflurane supplementation. In the saline solution group, only two patients did not need isoflurane at all. The end-tidal isoflurane concentrations required to maintain HR and arterial blood pressure within the predetermined limits are presented in Figure 2. The median expired concentration of isoflurane required during anesthetic maintenance was >90% less in the dexmedetomidine group (0.01 vol% [quartile deviation, QD 0.02]) compared with that in the saline solution group (0.17 vol% [QD 0.13]) (P = 0.01; 95% confidence interval for difference between median values −0.30 to −0.01). Furthermore, in dexmedetomidine-treated patients, supplemental isoflurane was required over a period that was significantly shorter than in the saline solution group (4.0 min [QD 6.0] vs 55.0 min [QD 39.5]) (P = 0.03; 95% confidence interval for difference between median values −86.0 to 0.0). Even though the study protocol obviously resulted in relatively light anes-

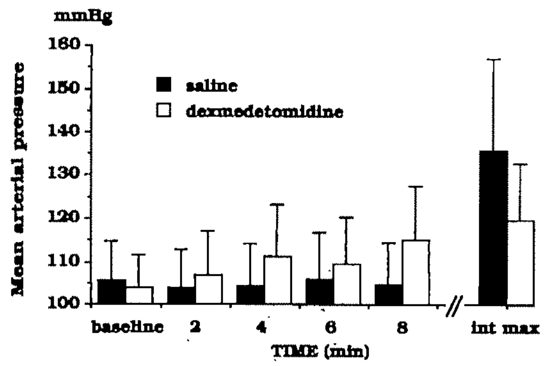

Figure 3. Mean arterial blood pressure (SD) during administration of the initial infusion (baseline) and the highest value obtained after endotracheal intubation (int max). During initial infusion, mean arterial blood pressure values were slightly higher in the dexmedetomidine group (RM ANCOVA, DRUG by TIME interaction; $P = 0.02$).

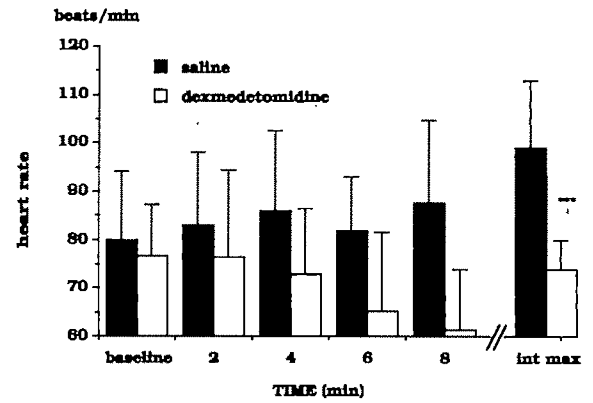

Figure 4. Mean heart rate (SD) during administration of the initial infusion (baseline) and the highest value obtained after endotracheal intubation (int max). ***$P < 0.001$ (t-test); dexmedetomidine differs from saline solution. During loading infusion, dexmedetomidine reduced heart rate (RM ANCOVA, DRUG by TIME interaction; $P < 0.001$).

thesia, none of the patients complained of intraoperative recall when interviewed on the first postoperative day.

Hemodynamic Variables

Baseline MAP values did not differ between groups (Figure 3). During administration of the initial infusion, the MAP values increased slightly in the dexmedetomidine group (~5 mm Hg), whereas in the saline solution group, MAP values remained at the same level ($P = 0.02$, drug by time interaction, RM ANCOVA). The highest MAP values after intubation (119 mm Hg [SD 13] in the dexmedetomidine group, 133 mm Hg [SD 22] in the saline solution group) were not significantly different. Intraoperatively, there were no differences in the arterial blood pressure values. Likewise, 1 h after surgery, the MAP values (82 mm Hg [SD 18] in the dexmedetomidine group and 85 mm Hg [SD 21] in the saline solution group) were similar.

Baseline HR values did not differ between groups (Figure 4). During the initial infusion, dexmedetomidine reduced HR significantly ($P < 0.001$; drug by time interaction, RM ANCOVA), compared with the saline solution group. The highest HR after intubation was lower in the dexmedetomidine group (74 beats/min [SD 6]) than in the saline solution group (99 beats/min [SD 14]) ($P < 0.001$). During the first hour after surgery, HR was significantly lower ($P = 0.05$; drug main effect, RM ANCOVA) in the dexmedetomidine group, and four patients in this group had HRs of <40 beats/min, requiring treatment with atropine (0.4 mg IV). None of the patients in the saline solution group required atropine treatment. There was no difference between the groups.

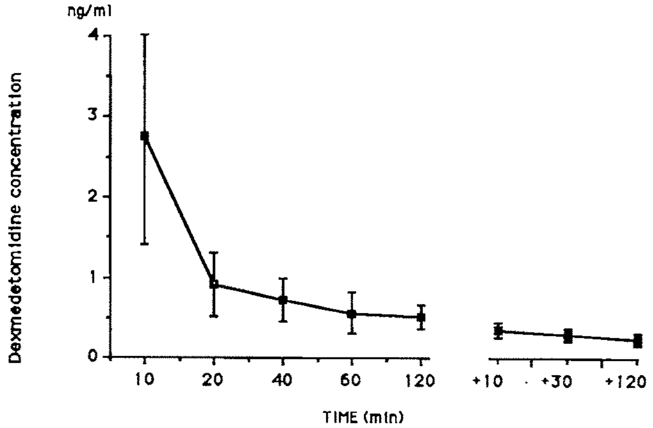

Figure 5. Mean (SD) dexmedetomidine concentration in peripheral arterial plasma versus time; +10, +30, and +120 are the concentrations obtained 10, 30, and 120 min after the end of infusion.

Dexmedetomidine Concentration

Dexmedetomidine plasma concentrations during the $170 + 10\text{-ng}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ infusion are presented in Figure 5.

Discussion

The major finding of this study was that the chosen continuous dexmedetomidine infusion was not potent enough to provide adequate maintenance of anesthesia when added to thiopental, fentanyl, and nitrous oxide in oxygen, but it did diminish isoflurane requirement during surgery by as much as 90%.

The anesthetic-sparing action of clonidine, a partial α_2-adrenergic agonist, has been previously demonstrated in several clinical investigations (6,9,10,11, 22). Clonidine affected isoflurane requirements less than dexmedetomidine in the present study. Ghignone et al. (6) demonstrated a 40% reduction in isoflurane requirements, using electroencephalography as an index of anesthetic depth, after oral premedication with 5 μg/kg of clonidine. More recently, an oral/transdermal clonidine combination was shown to diminish isoflurane demand by approximately 70% in patients undergoing abdominal surgery, when the inhaled anesthetic was administered using hemodynamic endpoints as criteria of anesthetic depth (22).

In contrast to clonidine, medetomidine and its active dextroisomer, dexmedetomidine, are full α_2-adrenergic agonists (23). Clonidine may not be the most appropriate choice because of its "ceiling effect" (4), followed by a reversal of the initial effect, which occurs at higher doses. This property is attributed to the partial agonistic effect of clonidine at the α_2-receptors (24), or to an α_1-agonistic effect (25). Thus, dexmedetomidine can be expected to be more efficacious in its anesthetic-sparing effect. In dogs receiving dexmedetomidine, the MAC for halothane decreased progressively, and at the highest intravenous dose of dexmedetomidine (10 μg/kg), the anesthetic requirement was reduced by >90% (4). Similarly, Segal et al. (5) showed that in rats, dexmedetomidine decreased halothane MAC in a dose-dependent fashion so that at 100 μg/kg intraperitoneally, halothane could be discontinued for up to 30 min without eliciting a purposeful response to tail-clamping (5). In contrast, with clonidine the maximal reduction in halothane MAC did not exceed 50% (26).

The sedative action of α_2-adrenoceptor agonists has been well recognized (27) to the extent that the sedative effect of clonidine has been a major problem in antihypertensive therapy (1). The site at which these drugs affect sleep mechanisms has been localized in the locus ceruleus (28). Actions other than synaptic norepinephrine depletion must be involved in the anesthetic effect of α_2-agonists, probably at a central postsynaptic α_2-adrenoceptor (5). This interaction could be explained by the fact that general anesthetics and α_2-agonists increase K^+ efflux (29–31) through neuronal cell membranes, causing hyperpolarization and decreased excitability of the neurons. This hyperpolarization may be mediated by a reduction in intracellular cyclic adenosine monophosphate (32), which is regulated through an inhibitory membrane-bound guanine nucleotide-binding protein (G-protein) (33).

Because of the lack of reliable, easily monitored clinical indices to determine anesthetic depth, we used hemodynamic endpoints. One can argue that such endpoints are not optimal, particularly when a hemodynamically active drug is studied. There is a possibility that the diminished isoflurane requirements may have partly been a result of the HR slowing by dexmedetomidine. However, in addition to hemodynamic endpoints, the signs of light anesthesia (e.g., bucking or lacrimation) were used as indicators of light anesthesia.

The MAP increased in a dose-dependent manner during the initial infusion before induction of anesthesia. Although this increase did not cause any untoward effects in our relatively healthy patients, those with preexisting vascular pathology should be studied separately. With a lower initial infusion rate or a longer infusion time, the increase in MAP could be avoided. Although hypertension induced by α_2-adrenergic agonists may have a relatively long duration in some animal models (34,35), the hypertensive response in humans seems to be of short duration and is rapidly overcome by the hypotensive action of α_2-agonists, mediated by α_2-adrenoceptors in the central nervous system (14,36). Pretreatment with a vagolytic glycopyrrolate might have enhanced the initial increase in arterial blood pressure.

The dexmedetomidine initial dose blunted the tachycardia in response to laryngoscopy and endotracheal intubation. A consistent feature of dexmedetomidine administration is the occurrence of bradycardia (14). This effect of dexmedetomidine was observed in our study during the initial infusion, lasting until 10 min after the induction of anesthesia. Thereafter, during the surgery HR was similar in both dexmedetomidine- and saline solution-treated patients. During the first postoperative hour, dexmedetomidine-treated patients again tended to have a lower HR, but the subsequent elimination of the drug and administration of atropine restored normal HR, so that 1 h after the operation, no differences were observed between groups.

Particular attention was paid to the maintenance of double-blindness of the study. After the dose-response study, we expected that the dexmedetomidine infusion would lead to a slight increase in MAP and a reduction in HR. Therefore, before induction, the patient was attended by the research nurse, and the anesthesiologist in charge remained unaware of the hemodynamic changes secondary to the initial dose.

α_2-Adrenergic agonists may provide an alternative to currently used anesthetic adjunctive agents owing to their anesthetic-sparing and hemodynamic stabilizing effects. Overall, the present results suggest that dexmedetomidine warrants further study to evaluate its possible usefulness in clinical anesthesia.

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Thermoregulatory Vasoconstriction During Propofol/Nitrous Oxide Anesthesia in Humans: Threshold and Oxyhemoglobin Saturation

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To determine the thermoregulatory effects of propofol and nitrous oxide, we measured the threshold for peripheral vasoconstriction in seven volunteers over a total of 13 study days. We also evaluated the effect of vasoconstriction on oxyhemoglobin saturation (Spo_2). Anesthesia was induced with an intravenous bolus dose of propofol (2 mg/kg), followed by an infusion of 180 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 15 min, and maintained with 60% nitrous oxide and propofol (80–160 $\mu g \cdot kg^{-1} \cdot min^{-1}$). Central and skin surface temperatures and Spo_2 (using two different pulse oximeters) were measured continuously; plasma propofol concentrations and arterial Po_2 were measured at 15-min intervals. Volunteers were cooled with a circulating water blanket until definitive peripheral vasoconstriction was detected. The tympanic membrane temperature triggering vasoconstriction was considered the thermoregulatory threshold. Vasoconstriction developed on seven study days during propofol/nitrous oxide anesthesia at a central temperature of 33.3 ± 1.0°C (mean ± SD) and plasma propofol concentration of 3.9 ± 1.1 μg/mL. The thresholds during anesthesia were significantly lower than those during the control period (36.7 ± 0.3°C), but the correlation between plasma propofol concentrations and vasoconstriction thresholds was poor. On the remaining six study days, vasoconstriction did not develop despite central temperatures ranging from 32.1 to 32.7°C. Corresponding propofol concentrations were 4.1–10.9 μg/mL. These data suggest that anesthesia with propofol, in typical clinical concentrations, and 60% nitrous oxide substantially inhibits thermoregulatory vasoconstriction. Vasoconstriction increased Spo_2 by approximately 2% without a significant concomitant change in Po_2. The observed increase in Spo_2 probably reflects decreased transmission of arterial pulsations to venous blood in the finger.

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Hypothermia is common during surgery and anesthesia and results from cold exposure and inhibition of thermoregulatory responses (1). Some protective responses against hypothermia, such as shivering and appropriate behavior, are prevented by anesthesia per se and muscle relaxation. Others, including active vasoconstriction, are centrally inhibited. For example, halothane and isoflurane decrease the threshold for vasoconstriction in humans (i.e., the central temperature triggering vasoconstriction) by 1–3°C in a dose-dependent fashion (2–5).

Some intravenous anesthetics, including barbiturates (6), profoundly inhibit thermoregulatory responses in animals; others, such as ketamine (7,8), urethane (9,10), and fentanyl/droperidol (11), appear to have less effect. Barbiturates also appear to inhibit thermoregulatory responses in humans (12). Thermoregulatory effects of intravenous anesthetics have not been extensively investigated in humans, but fentanyl alone (13) and fentanyl combined with nitrous oxide (14) do inhibit responses. Propofol is a recently introduced anesthetic; however, the thermoregulatory consequences of its administration have not been quantified. Accordingly, we tested the hypothesis

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that propofol/nitrous oxide anesthesia inhibits thermoregulatory vasoconstriction in humans.

We (15) and others (16) have observed that thermoregulatory vasoconstriction increases oxyhemoglobin saturation (SpO_2) 1%–2%. However, alterations in SpO_2 produced by thermoregulatory vasoconstriction have not been correlated with changes in arterial PO_2. We therefore measured arterial PO_2 and SpO_2 (using two brands of pulse oximeter) and tested the hypothesis that thermoregulatory vasoconstriction increases systemic arterial PO_2.

Methods

After receiving approval from the University of California, San Francisco, Committee on Human Research, we studied seven volunteers over a total of 13 study days. None of the volunteers was obese, taking medication, or had a history of thyroid disease, dysautonomia, or Raynaud's syndrome. Ambient temperature was maintained at 20.9 ± 0.3°C (mean ± SD) and ambient relative humidity at 42% ± 3% throughout the study period (model HX93 humidity and temperature transmitter, Omega Engineering). The percentage of body fat in each volunteer was determined using infrared interactance (Futrex 1000, Futrex, Inc., Hagerstown, Md.) (17).

Study Protocol

Volunteers fasted during the 8 h preceding each study, which started at approximately 9:30 AM. All were minimally clothed and reclined on a standard operating room table covered by a full-length circulating water mattress set at 37°C (Blanketrol, Cincinnati Sub-Zero Products, Inc., Cincinnati, Ohio). An intravenous catheter was inserted into the left antecubital vein, and lactated Ringer's solution warmed to 37°C was infused at approximately 100 mL/h. A 20-gauge catheter was inserted into the left radial artery to permit sampling of blood for determination of circulating drug concentrations.

After a 15-min control period, anesthesia was induced without any premedication by administration of an intravenous bolus dose of propofol (ICI Americas, Inc., Wilmington, Del.) (2 mg/kg), followed by an infusion of 180 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 15 min. Neither thiopental nor opioids were administered. Vecuronium (10 mg IV) was administered to facilitate intubation of the trachea. Anesthesia was maintained with 60% nitrous oxide and an infusion of propofol at a rate of 80, 100, 120, or 160 $\mu g \cdot kg^{-1} \cdot min^{-1}$ delivered by a Program 2 syringe pump (Becton Dickinson & Company, Lincoln Park, N.J.); maintenance infusion rates were kept constant throughout each study day. Different infusion rates were used to produce a range of clinically relevant blood propofol concentrations (18).

Four volunteers were studied on more than one day. Of these, two were studied with three different propofol infusion rates: 80, 100, and 160 $\mu g \cdot kg^{-1} \cdot min^{-1}$. One other volunteer was studied at 80 and 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$, and a fourth was studied at 120 and 160 $\mu g \cdot kg^{-1} \cdot min^{-1}$.

Muscle relaxation was maintained with an infusion of vecuronium (Program 2 syringe pump) adjusted to maintain 0–1 twitches in response to supramaximal train-of-four electrical stimulation of the ulnar nerve at the wrist. Mechanical ventilation was adjusted to maintain end-tidal PCO_2 at 34 ± 1 mm Hg, and inspired oxygen concentration was maintained at 30% (monitored by a Capnomac [Datex Medical Instrumentation, Inc., Tewksbury, Mass.]). Routine monitoring throughout the study included arterial blood pressure and heart rate.

After an initial 45 min, central hypothermia was induced by decreasing the circulating water blanket temperature to 10°C. Anesthesia was discontinued when (a) definitive thermoregulatory vasoconstriction was observed; (b) central temperature approached 32°C without evidence of developing vasoconstriction; or (c) 6 h of anesthesia elapsed.

Measurements

Temperatures were monitored continuously with Mon-a-Therm (St. Louis, Mo.) thermocouple probes connected to Mallinckrodt model 8700 (St. Louis, Mo.) two-channel electronic thermometers. One thermocouple probe was placed in contact with the tympanic membrane and the aural canal was carefully occluded with cotton. After induction of anesthesia, temperatures also were recorded from the distal fourth of the esophagus by means of a probe incorporated into an esophageal stethoscope. Because our study design required central temperature measurements before induction of anesthesia, we considered tympanic membrane temperatures to be representative of central tissues. We (3,19) and others (20,21) have previously demonstrated an excellent correlation between distal esophageal and tympanic membrane temperatures. Skin temperature was measured at 10 sites and the area-weighted mean calculated by assigning the following regional percentages: head 6%, upper arms 9%, forearms 6%, hands 4.5%, back 19%, chest 9.5%, abdomen 9.5%, thigh 19%, calves 11.5%, and feet 6% (22).

Skin-temperature gradients were used to measure thermoregulatory vasoconstriction on the right arm. The gradient was calculated by subtracting fingertip skin temperature from midforearm skin temperature. Fingertip temperature can range from near ambient (vasoconstricted) to near core temperature (vasodilated) because of the presence of thermoregulatory arteriovenous shunts and the wide range over which fingertip blood flow varies. Forearm skin does not possess arteriovenous shunts, and therefore its temperature is less affected by thermoregulatory status. We have previously demonstrated that forearm minus fingertip skin-temperature gradients correlate extremely well with volume plethysmography (the most reliable measure of peripheral blood flow) (23). There is also a fair correlation between skin temperature gradients and laser Doppler flowmetry (4,14). The right arm was kept well away from the circulating water blanket and had neither an intravenous catheter nor a blood pressure cuff. As in previous studies, a forearm minus fingertip skin-temperature gradient exceeding 4°C was considered definitive vasoconstriction (2,3,14).

Fingertip Sp_{O_2} was monitored continuously with Nellcor N200 (Hayward, Calif.) and Lifestat 1600 (Physio-Control, Redmond, Wash.) pulse oximeters placed on fingers of the right hand. Central and skin temperatures and Sp_{O_2} were recorded at 5-min intervals using a previously described data-acquisition system (24).

Arterial blood samples were drawn at 15-min intervals, and P_{O_2} was determined using a calibrated Stat Pro 3 (Nova Biomedical, Waltham, Mass.) whole-blood gas analyzer. Blood for propofol determinations was centrifuged and the plasma stored frozen for later analysis. Samples were analyzed using high-pressure liquid chromatography (PharmaKinetics Laboratories, Inc., Baltimore, Md.). This assay has an accuracy >0.1 μg/mL for concentrations ranging from 0.1 to 5.0 μg/mL and an accuracy >0.2 μg/mL for concentrations ranging from 5.0 to 10.0 μg/mL.

Data Analysis

The thermoregulatory threshold for vasoconstriction was defined as the tympanic membrane (central) temperature at which definitive vasoconstriction was first observed. A data-base program was used to average the Sp_{O_2} and P_{O_2} values in each volunteer during the 15-min epoch before and after vasoconstriction. Vasoconstriction thresholds before induction of anesthesia and during propofol/nitrous oxide administration were compared using two-tailed, paired *t*-tests. The correlation between vasoconstriction thresholds and blood propofol concentrations was evaluated using linear regression. Time-dependent changes in Sp_{O_2} and P_{O_2} were analyzed using repeated-measures analysis of variance and Dunnett's tests. Measurements obtained 10–20 min after vasoconstriction were used as the reference for determining statistically significant changes. Differences were considered significant when $P \leq 0.01$. Results are reported as mean ± SD.

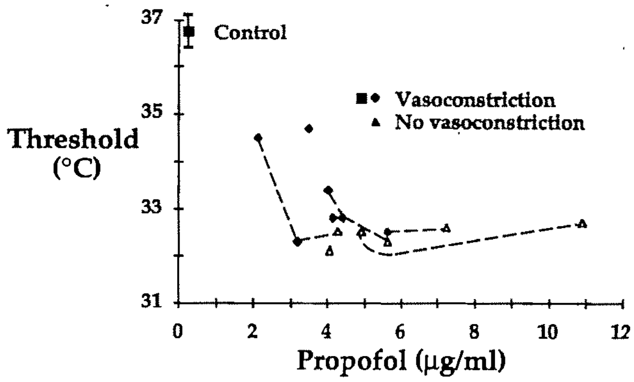

Figure 1. On 7 of 13 study days, vasoconstriction developed during propofol/N$_2$O anesthesia at central temperatures between 32.3 and 34.7°C (*solid diamonds*, 33.3 ± 1.0°C), when plasma propofol concentrations were between 2.1 and 5.6 μg/mL (3.9 ± 1.1 μg/mL). The thresholds during anesthesia were significantly lower than those during the control period (*solid square*, 36.7 ± 0.3°C). Plasma propofol concentrations correlated poorly with vasoconstriction thresholds (Threshold = 35.1 − 0.8[Propofol]; r = 0.53). On the remaining six study days, vasoconstriction did not develop despite central temperatures ranging from 32.1 to 32.7°C, with propofol concentrations of 4.1–10.9 μg/mL (*open triangles*). *Dashed lines* connect data for individuals who participated on more than one study day.

Results

The mean age of the volunteers was 25.9 ± 2 yr, weight 74 ± 15 kg, height 176 ± 7 cm, and body fat 19% ± 3%. Tympanic membrane and distal esophageal temperatures were typically within 0.1°C and rarely differed by >0.2°C.

All volunteers experienced vasoconstriction during the control period before induction of anesthesia. Vasoconstriction developed during propofol/nitrous oxide anesthesia on 7 of the 13 study days at central temperatures between 32.3 and 34.7°C (mean 33.3 ± 1.0°C) (Figure 1). The corresponding mean skin temperature was 27.2 ± 1.0°C, and plasma propofol concentrations ranged from 2.1 to 5.6 μg/mL (mean 3.9 ± 1.1 μg/mL). The vasoconstriction threshold during anesthesia on these seven study days was significantly lower than the threshold during the control period, when central temperature was 36.7 ± 0.3°C and mean skin temperature was 31.1 ± 0.7°C. The correlation between plasma propofol concentrations and thresholds for vasoconstriction was poor (Threshold = 35.1 − 0.8[Propofol]; r = 0.53).

On the remaining six study days, vasoconstriction did not develop despite central hypothermia to between 32.1 and 32.7°C and mean skin temperatures of 27.9 ± 1.6°C (Figure 1). Plasma propofol concentrations measured at the lowest central temperature

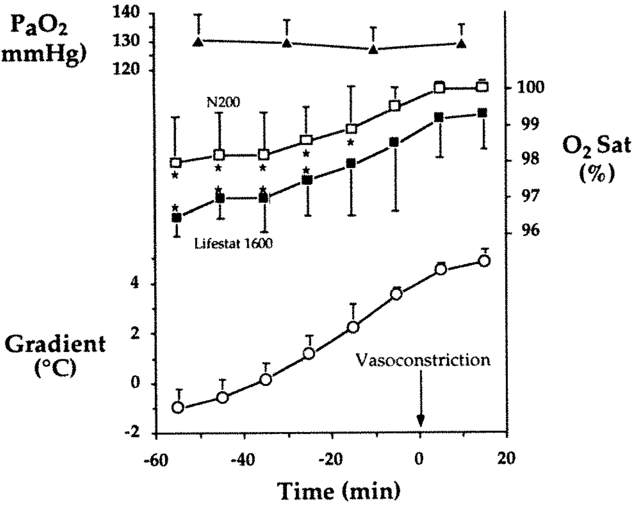

Figure 2. Arterial Po_2 (Pao_2) did not change significantly during vasoconstriction; however, Spo_2 (O_2 Sat) readings from both the Nellcor N200 and the Physio-Control Lifestat 1600 pulse oximeters increased approximately 2%. The time axis is normalized so that definitive thermoregulatory vasoconstriction (a skin temperature gradient = 4°C) occurred at time zero. *Spo_2 values significantly different from those after vasoconstriction (10–20 elapsed min).

before rewarming were generally higher (6.2 ± 2.6 μg/mL [range 4.1–10.9]) than those measured at the time of vasoconstriction during the other seven study days ($P = 0.053$).

In those volunteers who were studied at more than one infusion rate, higher infusion rates were associated with increased plasma propofol levels and either lower thresholds for vasoconstriction or no vasoconstriction at all (Figure 1).

Arterial Po_2 and Spo_2 data from both oximeters were available on only five of the seven study days when vasoconstriction occurred. Thermoregulatory vasoconstriction increased Spo_2 1.7% ± 1.4% on the Nellcor N200 and 2.3% ± 1.6% on the Lifestat 1600. There were no significant changes in arterial Po_2, arterial blood pressure, or heart rate at the time of vasoconstriction (Figure 2).

Discussion

Physiologic responses to MAC-adjusted concentrations of various volatile anesthetics are more notable for their similarities than differences. For example, the thresholds for thermoregulatory vasoconstriction appear only slightly higher during halothane (2) than during isoflurane anesthesia (3). In contrast, thermoregulatory responses to intravenous anesthetics, sedatives, and hypnotics differ considerably (6,7,11,13), making it difficult to predict responses to a new drug without specific experimental evidence.

Our data indicate that anesthesia with propofol in typical clinical concentrations, combined with 60% nitrous oxide, substantially inhibits thermoregulatory vasoconstriction. Although the correlation between propofol concentration and vasoconstriction threshold calculated from the combined data was poor, a dose-dependent effect is apparent from the data obtained from those volunteers given more than one propofol infusion rate. Furthermore, plasma propofol concentrations were generally higher on study days when vasoconstriction did not develop than on days when it did. Presumably, vasoconstriction would have developed in all cases were volunteers permitted to become sufficiently hypothermic. For safety reasons, we rewarmed volunteers when their central temperatures reached 32°C. Clinically, it is rare for patients to become this hypothermic without deliberate cooling.

Poor correlation between propofol concentrations and vasoconstriction thresholds may have resulted because the apparently steep dose-response relationship allowed only a small number of data points to fall within the relatively narrow range of permissible central temperatures. Had we allowed central temperature to decrease sufficiently to trigger vasoconstriction in all cases, the correlation may have been better.

The range of thermoregulatory thresholds in those volunteers who experienced vasoconstriction during propofol/nitrous oxide anesthesia was 32.3–34.7°C, which is similar to the range of thresholds expected from administration of 0.8%–1.7% end-tidal isoflurane (3) and lower than the range observed during anesthesia with 0.86% halothane or 70% nitrous oxide and fentanyl 4 $\mu g \cdot kg^{-1} \cdot h^{-1}$ (2,14).

Nitrous oxide contributed approximately 0.6 MAC in these volunteers. Although nitrous oxide combined with fentanyl significantly inhibits thermoregulatory vasoconstriction (14), the effect of nitrous oxide alone on vasoconstriction has not specifically been determined. Subanesthetic partial pressures of nitrous oxide impair behavioral thermoregulatory responses in mice (25). Similarly, 30% nitrous oxide decreases the shivering threshold approximately 1°C in humans (26). It is thus likely that nitrous oxide also inhibits thermoregulatory vasoconstriction; however, its contribution to the observed profound inhibition with propofol cannot be determined from our data.

The tympanic membrane is not an obvious site for measuring central temperature; it is a small structure, surrounded by air and does not have a particularly high blood flow. Tympanic membrane temperature measurements were popularized by Benzinger (27) in 1959. (In a remarkable investigation, he demonstrated the validity of tympanic membrane temperatures by having thermometers implanted into his own head!) Numerous subsequent studies have demonstrated superb correlations between distal esophageal and tympanic membrane temperatures (3,19–21).

Many mammals possess specialized vascular systems that allow them to maintain a lower brain temperature than core temperature (28). Recently, Cabanac and Caputa (29) have proposed that humans may also have specific brain cooling. The major support for this thesis is an observed decrease in tympanic temperature relative to distal esophageal temperature during heat stress and facial fanning (30,31). (The assumption in these studies is that the apparent relative decrease in tympanic membrane temperature represents true brain cooling, not simply an artifact of the measurement location.) However, even during these special circumstances, the distal esophageal to tympanic membrane temperature difference rarely exceeds 0.2°C. Under circumstances similar to our study (i.e., gradual cooling without facial fanning), the two temperatures usually are virtually identical.

Because of the observed small differences between tympanic membrane and other central temperature measurement sites under some circumstances, most physiologists now prefer distal esophageal temperatures. During general anesthesia, the distal esophagus is usually the easiest and most reliable central temperature monitoring site. However, during the control period, we recorded only tympanic membrane temperatures because esophageal probes would have been uncomfortable for unanesthetized subjects. Consequently, the vasoconstriction thresholds in this study are reported in terms of tympanic membrane temperature to minimize systematic errors. In any case, potential errors in our central temperature measurements are of little consequence compared with the range of thresholds observed in this study.

Our volunteers were not undergoing surgery or comparable pain. Painful stimulation provided by a 100-Hz current increases the thermoregulatory threshold only approximately 0.4°C during enflurane anesthesia (32). However, the extent to which pain and subsequent autonomic activation contribute to thermoregulatory responses during propofol/nitrous oxide anesthesia remains unknown. Therefore, our current results may not necessarily apply to patients during surgery. Nevertheless, in patients whose surgical pain is prevented by regional anesthesia, propofol/nitrous oxide anesthesia would likely produce similar thermoregulatory inhibition.

As in our previous study (15), fingertip pulse oximetry significantly increased Sp_{O_2}. Mean arterial blood pressure remained within the normal range during our study and did not change significantly during vasoconstriction. We have already demonstrated that pulse oximeters continue to function well, even when arterial inflow (33) or venous outflow (34) is substantially reduced.

Systemic or local pulmonary hypothermia impairs hypoxic pulmonary vasoconstriction (35) and would be expected to increase pulmonary shunt and decrease arterial P_{O_2}. However, we speculated that pulmonary blood flow distribution may be altered in conjunction with the activation of thermoregulatory peripheral vasoconstriction, thus leading to an actual increase in arterial P_{O_2}. Nevertheless, our data indicate that no significant changes in arterial P_{O_2} occurred. It is therefore unlikely that the increase in Sp_{O_2} observed with both oximeters resulted from a systemic effect of hypothermia.

More likely, the increase in Sp_{O_2} was caused by a decrease in the venous pulsatile signal resulting from the closure of arteriovenous shunts, as proposed by Kelleher and Ruff (16). Normal (vasodilated) finger blood flow exceeds nutritive requirements more than 10-fold, with most of the volume traversing arteriovenous shunts (36). Because these are relatively large vessels (100 μm), it is likely that arterial pulsations extend to venules just distal to the shunts. However, some of this distal blood is desaturated (having passed through capillaries) and will reduce the apparent arterial saturation (37). After vasoconstriction, fingers resemble most other tissues in that arterial pulsations do not extend to the venous circulation, and pulsatile flow is nearly entirely arterial. As pulse oximeters detect only pulsatile flow, apparent saturation would increase after vasoconstriction.

Manufacturers of pulse oximeters calibrate their devices empirically using data obtained from human subjects. Our results suggest that this calibration would be affected by the thermoregulatory status of those volunteers. It is important to note that this approximately 2% effect may be seen in a large percentage of patients recovering from general anesthesia, because even mild intraoperative hypothermia usually produces intense vasoconstriction on arrival in the postanesthesia care unit.

In summary, on 7 of 13 study days, vasoconstriction developed during propofol/nitrous oxide anesthesia at central temperatures of 33.3 ± 1.0°C and plasma propofol concentrations of 3.9 ± 1.1 μg/mL. Vasoconstriction thresholds during anesthesia were significantly lower than those during the control period (36.7 ± 0.3°C), but the correlation between plasma propofol concentrations and these thresholds was poor. On the remaining six study days, vasoconstriction did not develop, even though central temperatures ranged from 32.1 to 32.7°C, with propofol concentrations of 4.1–10.9 μg/mL. Fingertip Sp_{O_2} measured with two different pulse oximeter models increased approximately 2% during thermoregulatory vasoconstriction without a concomitant increase in arterial PO_2. We conclude that general anesthesia with typical clinical concentrations of propofol combined with 60% nitrous oxide substantially inhibits thermoregulatory vasoconstriction and that vasoconstriction artifactually increases SpO_2.

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Alfentanil-Induced Hypermetabolism, Seizure, and Histopathology in Rat Brain

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We evaluated the effect of alfentanil on hippocampal glucose utilization and histopathology associated with alfentanil-induced seizures. Three separate experiments were performed. First, anesthetized, paralyzed Long-Evans rats ($n = 15$; 5 rats per group) were mechanically ventilated and randomly assigned to three groups: (a) control, 70% N_2O and 30% O_2 continued for 1 h; (b) low-dose alfentanil (150 $\mu g/kg$ IV bolus), followed by infusion at 15 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 1 h without N_2O; or (c) high-dose alfentanil (1000 $\mu g/kg$ IV bolus), followed by infusion at 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 1 h without N_2O. After 1 h, [6-^{14}C]glucose was injected intravenously for autoradiography. With high-dose alfentanil, there was increased glucose utilization in the ventral hippocampus and the lateral septal nucleus. In the second experiment, anesthetized, paralyzed Sprague-Dawley rats ($n = 12$; 4 rats per group) were mechanically ventilated, underwent insertion of hippocampal depth electrodes, and were randomly assigned to three groups: (a) control, 70% N_2O and 30% O_2; (b) low-dose alfentanil (150 $\mu g/kg$ IV bolus), with 70% N_2O and 30% O_2; or (c) high-dose alfentanil (1000 $\mu g/kg$ IV bolus), with 70% N_2O and 30% O_2. An epileptiform pattern was observed on hippocampal and subdermal electroencephalographic recordings in both alfentanil groups. In the third experiment, anesthetized, paralyzed Sprague-Dawley rats ($n = 20$) were mechanically ventilated and assigned to two groups: (a) control, 70% N_2O and 30% O_2 ($n = 5$) or 100% O_2 ($n = 5$) continued for 1 h; or (b) alfentanil (2000 $\mu g/kg$ IV bolus), followed by infusion at 33.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 1 h with 100% O_2. After tracheal extubation, the rats recovered overnight. Light-microscopic evaluation revealed hippocampal or amygdaloid damage in 6 of the 10 alfentanil-treated rats. High doses of alfentanil administered to rats can produce limbic system seizure activity with hypermetabolism associated with neuropathologic lesions.

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Epileptiform activity with increased metabolic rate in hippocampal foci has been reported in rats given large intravenous (IV) doses of fentanyl (1) or sufentanil (2) or intracerebroventricular injections of other opiate receptor agonists (3,4). Seizures produce neuropathologic lesions in areas of hypermetabolism (5,6). We designed studies to test the hypotheses that large IV doses of alfentanil in rats would produce (a) an increased hippocampal metabolic rate, (b) an epileptiform pattern on both subdermal and hippocampal electroencephalograms (EEG), and (c) histopathologic lesions in the limbic system. The data presented here support these hypotheses.

Methods

Three sequential studies were performed at two institutions: (a) glucose utilization experiments (Hershey Medical Center), (b) hippocampal depth-electrode recordings (University of Pittsburgh), and (c) histologic investigations (University of Pitts-

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This work was presented in part at the 1989 Annual Meetings of the Society for Neuroscience, Phoenix, Arizona, and the Society of Neurologic Anesthesia and Critical Care, New Orleans, Louisiana, and at the 1991 meetings of the Society for Neuroscience, New Orleans, Louisiana, and the Society of Neurologic Anesthesia and Critical Care, San Francisco, California.

This work was performed in the laboratories of the Department of Anesthesia, Milton S. Hershey Medical Center, Pennsylvania State University, Hershey; Departments of Anesthesiology/Critical Care Medicine and Pathology, University of Pittsburgh School of Medicine, Pittsburgh; and Consultants in Veterinary Pathology, Monroeville, Pennsylvania.

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burgh). Approvals of the Institutional Animal Care Committees were obtained for all experiments.

Glucose Utilization Experiments

Fifteen Long-Evans rats weighing 250–350 g were fasted overnight. Anesthesia was induced with 5% halothane in O_2 for 3 min, followed by an intramuscular injection of *d*-tubocurarine (0.45 mg), and the trachea was intubated with a 14-gauge Teflon catheter. The rats' lungs were then mechanically ventilated (Analytical Specialties ventilator, St. Louis, Mo.) for the remainder of the experiment, and inspired and expired O_2, CO_2, N_2O, and halothane were continuously monitored by mass spectrometry (Perkin Elmer, Pittsburgh, Pa.) (7). The rats were then mechanically ventilated to maintain a constant end-tidal P_{CO_2}. Biparietal subdermal electroencephalographic (EEG) needle electrodes and a rectal temperature probe were inserted. A femoral vein and artery were cannulated, and arterial blood pressure was continuously monitored. Anesthesia during surgery consisted of 70% N_2O and 1% halothane. Halothane was discontinued on completion of surgery, and sedation was then maintained with 70% N_2O and 30% O_2 for 1 h (no painful procedures were performed during this time). Heparin (200 U) was administered intravenously.

Each rat was randomly assigned to one of three groups: control, low-dose alfentanil, or high-dose alfentanil ($n = 5$ per group). The control group continued to receive the N_2O/O_2 mixture for 1 h, and 0.9% saline was infused intravenously at 4 $mL \cdot kg^{-1} \cdot h^{-1}$. The low-dose group received an intravenous bolus dose of alfentanil (150 μg/kg) over 1–2 min, followed by an infusion of 15 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 1 h. (In rats, this dose approximates the sedation level achieved with 70% N_2O [8].) The high-dose group received an intravenous bolus dose of alfentanil (1000 μg/kg) over 1–2 min, followed by an infusion of 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 1 h. In the low- and high-dose groups, N_2O was discontinued simultaneously with administration of the bolus dose of alfentanil. At the end of 1 h, 0.2 mL of blood was withdrawn for analysis of plasma glucose. Then, 35 μCi of [6-^{14}C]glucose was injected intravenously over 8–10 s, and 0.2–0.5-mL arterial samples were withdrawn at 30 s and 1, 2, 3, and 4 min. The radiolabeled glucose was injected through a venous cannula that was used only for that purpose and for an intravenous injection of a cardioplegic dose (150 mg) of pentobarbital at 5 min.

The brain was quickly removed and suspended in a two-phase solution of 1-methylbutane and 2-bromobutane chilled to −30°C in Freon-12. Coronal sections (40 μm) were cut, melted onto glass slides, dried at 55°C, and exposed for 20 days to radiographic film (low-dose mammography film, EI DuPont DeNemours, Wilmington, Del.) along with a set of calibrated ^{14}C-methylmethacrylate standards. Optical densities were measured with a pinhole densitometer (Tobias, Ivyland, Pa.) for determination of the cerebral metabolic rate for glucose (CMRgl) in 63 discrete regions. Brain regions were identified using an atlas of the rat brain (9). Regional CMRgl was then calculated using procedures previously described (10,11). Regional brain glucose concentrations were not measured. The brain/plasma glucose ratio was assumed to be 0.2 (10,11). The coefficient of variation for this technique is 12%, and the sample sizes in this experiment were sufficiently large to reveal CMRgl differences of 0.08–0.32 $\mu mol \cdot 100\ g^{-1} \cdot min^{-1}$.

To examine beyond the 63 discrete areas, three-dimensional imaging techniques of CMRgl throughout the brain were used in one control and one high-dose rat (12).

Assays. Glucose was measured spectrophotometrically with hexokinase and glucose 6-phosphate dehydrogenase in neutralized perchloric acid extracts of plasma (13). Plasma radioactivity was determined by liquid scintillation counting. The coefficient of variation for this assay is 16%. The sample sizes used allowed determination of differences in blood glucose of 8–40 mg%.

Chemicals. Alfentanil hydrochloride (for all three experiments) dissolved in isotonic saline (Alfenta, 500 μg/mL) was obtained from Janssen Pharmaceutica (Piscataway, N.J.). Enzymes and coenzymes were supplied by Boerhinger-Mannheim Corporation (New York, N.Y.). [6-^{14}C]glucose (6.8 mCi/mmol) was obtained from Amersham (Arlington Heights, Ill.).

Statistical analysis. Multivariate analysis of variance (ANOVA) was used to compare CMRgl in five hippocampal regions by brain area and by anesthetic group (14). Univariate ANOVA was used to test CMRgl in all of the remaining brain areas. In areas with significant F ratios, least-significant difference tests were used for pairwise comparisons of anesthetic groups. Differences were considered to be significant at $P < 0.05$.

Hippocampal Depth-Electrode Recordings

Twelve male Sprague-Dawley rats weighing 300–450 g were allowed access to food and water overnight. Anesthesia was induced with 5% halothane in 70% N_2O and 30% O_2, and the trachea was intubated with a 14-gauge Teflon catheter. The lungs were then mechanically ventilated (Analytical Specialties ventilator) for the remainder of the experiment, and inspired and expired O_2, CO_2, N_2O, and halothane were continuously monitored by Raman spectrometry (Ohmeda, Salt Lake City, Utah) (7). Mechanical ventilation was adjusted to maintain constant end-tidal CO_2. Pancuronium (0.6 mg IV) was administered as needed to prevent movement. A femoral vein and artery were cannulated, and arterial blood pressure was continuously monitored. A rectal temperature probe was inserted. The rat was placed in a stereotaxic frame, a burr hole was made, and a bipolar EEG electrode was inserted into the dentate gyrus at the following coordinates (15): rostrocaudal, −3.3 mm (relative to the bregma); mediolateral, 1.8 mm right; dorsoventral, 3.3 mm (relative to the dura). The dentate gyrus was chosen for electrode placement because evidence indicates that this region exerts a critical regulatory role in the passage of paroxysmal activity through hippocampal circuits (16). Anesthesia during surgery consisted of 1%–2% halothane in 70% N_2O and 30% O_2. Halothane was discontinued on completion of surgery, and sedation was maintained with 70% N_2O and 30% O_2 for the remainder of the experiment.

After 1 h, each rat was randomly assigned to one of three groups: control, low-dose alfentanil, or high-dose alfentanil ($n = 4$ per group). Control rats were given 0.9% saline (2 mL/kg IV). The low-dose group received an intravenous bolus dose of alfentanil (150 μg/kg) plus 0.9% saline to a total volume of 2 mL/kg over 1 min. The high-dose group received an intravenous bolus dose of alfentanil (1000 μg/kg) to a total volume of 2 mL/kg over 1 min. Nitrous oxide was continued because of concerns that the epileptiform activity seen in glucose utilization studies could be exacerbated by hyperoxia (17) and N_2O withdrawal (18). Subdermal and hippocampal EEGs were recorded for 30 min after injection of alfentanil or saline in all rats. Thirty minutes after opioid injection, arterial blood gas tensions and blood glucose levels were determined, and animals were then killed with aortotomy under deep halothane anesthesia.

Histologic Examinations

Twenty male Sprague-Dawley rats weighing 250–350 g were allowed access to food and water overnight. Anesthesia was induced with 5% halothane in 70% N_2O and 30% O_2; the trachea was intubated with a 14-gauge Teflon catheter; and 0.6 mg of pancuronium was injected intravenously as often as needed to maintain neuromuscular blockade. The lungs were then mechanically ventilated (Analytical Specialties ventilator) for the duration of the opioid administration and up to 3 h afterward, and inspired and expired O_2, CO_2, N_2O, and halothane were continuously monitored by Raman spectrometry (Ohmeda) (7). Mechanical ventilation was adjusted to maintain constant end-tidal CO_2. Biparietal subdermal needle electrodes and a rectal temperature probe were inserted. A femoral vein and artery were cannulated, and arterial blood pressure was continuously monitored. Anesthesia during surgery consisted of 1.5% halothane in 70% N_2O and 30% O_2. Halothane was discontinued on completion of surgery, and sedation was maintained with 70% N_2O and 30% O_2 for 1 h.

After 1 h, each rat was randomly assigned to one of two groups: control or high-dose alfentanil. In the alfentanil group, an intravenous bolus dose of alfentanil (2000 μg/kg) was administered over 1–2 min, followed by an infusion of 33.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 1 h (twice the loading dose used in the CMRgl and EEG experiments). As the bolus dose was injected, N_2O was discontinued and replaced by O_2. The first five control rats received 100% O_2 with 0.9% saline administered intravenously at 4 $mL \cdot kg^{-1} \cdot h^{-1}$ for 1 h, and the second five control rats continued to receive the N_2O/O_2 mixture, with 0.9% saline solution administered intravenously at 4 $mL \cdot kg^{-1} \cdot h^{-1}$ for 1 h. (The initial experimental design called for randomization of five hyperoxic control and five alfentanil-treated rats. However, after observing brain damage in two of the alfentanil-treated rats, we repeated the study using five N_2O-treated control and five alfentanil-treated rats to control for the possible influence of hyperoxia [17] and N_2O withdrawal [18] on brain injury. No difference in brain damage was evident between the two series of experiments [i.e., that with hyperoxic controls versus that with N_2O-treated controls]. Thus, the groups were combined [10 controls, 10 alfentanil treated].) After 1 h of anesthetic or control, all rats received 100% O_2 and underwent extubation when alert. They were placed in an O_2-infused enclosure for 1 h and then moved to a cage overnight.

Approximately 18 h after the anesthetic or control period, the rats were anesthetized with halothane and underwent cerebral perfusion-fixation with 10% neutral buffered formalin via a thoracotomy with left ventricular cannulation. The calvaria were removed, and the exposed brains were further immersion fixed in neutral buffered formalin for at least 24 h before their removal. The brains were sliced at approximately 3-mm intervals and the slices embedded in paraffin by routine techniques. Six-micrometer sections of each brain block were prepared, stained with hematoxylin and eosin, and evaluated by light microscopy. Degrees of neuropathologic alterations within a given anatomic region were based on subjective assessment of the number and distribution of eosinophilic neurons and severity of tissue edema.

Table 1. Physiologic Variables

Study group	MAP (mm Hg)	Pao$_2$ (mm Hg)[a]	Paco$_2$ (mm Hg)	pHa	T_R (°C)	Glucose (mg%)
Glucose Utilization Experiments[b]						
Control	134 ± 12	133 ± 12	38 ± 2	7.36 ± 0.03	37.9 ± 0.1	71 ± 4
Low-dose alfentanil	133 ± 3	379 ± 55	41 ± 2	7.34 ± 0.03	38.1 ± 0.1	73 ± 10
High-dose alfentanil	140 ± 3	397 ± 26	40 ± 2	7.35 ± 0.02	38.1 ± 0.1	72 ± 9
Hippocampal Depth-Electrode Recordings[c]						
Control	144 ± 23	150 ± 4	31 ± 1	7.41 ± 0.03	37.0 ± 0.2	100 ± 9
Low-dose alfentanil	151 ± 8	139 ± 3	34 ± 2	7.40 ± 0.02	37.5 ± 0.2	96 ± 6
High-dose alfentanil	140 ± 7	140 ± 6	33 ± 1	7.42 ± 0.01	37.1 ± 0.1	101 ± 2
Histologic Investigation[d]						
Before alfentanil infusion						
Control	144 ± 5	143 ± 4	30 ± 2	7.46 ± 0.01	37.6 ± 0.2	104 ± 6
High-dose alfentanil	144 ± 3	149 ± 4	27 ± 2	7.45 ± 0.02	37.8 ± 0.1	97 ± 6
During alfentanil infusion						
Control	155 ± 4	302 ± 60	32 ± 2	7.42 ± 0.01	37.8 ± 0.2	123 ± 7
High-dose alfentanil	158 ± 5	478 ± 13	31 ± 2	7.40 ± 0.01	37.8 ± 0.02	101 ± 5
After alfentanil infusion						
Control	155 ± 4	317 ± 57	31 ± 2	7.40 ± 0.01	38.0 ± 0.1	114 ± 7
High-dose alfentanil	145 ± 4	435 ± 18	30 ± 3	7.39 ± 0.02	38.0 ± 0.1	106 ± 7

MAP, mean arterial blood pressure; T_R, rectal temperature; pHa, arterial pH; Pao$_2$, arterial Po$_2$; Paco$_2$, arterial Pco$_2$.

[a] Significant difference between groups for Pao$_2$.

[b] Values were measured at the time of administration of [6-^{14}C]glucose and are mean ± SEM; $n = 5$ for each group.

[c] Values were measured just before injection of alfentanil or saline solution (control); $n = 4$ for each group.

[d] Values were measured 15 min before alfentanil infusion, 30 min after the start of alfentanil infusion, and 30 min after the termination of alfentanil infusion; $n = 10$ for each group.

Scores were assigned by a pathologist, who was unaware of the experimental treatment, as follows: 0 = none, 1 = minimal, 2 = mild, 3 = moderate, 4 = marked, and 5 = severe. These grades are semiquantitative in that they reflect the approximate percentage of degenerating neurons present in an affected neuroanatomic area as follows: 1 (<5%), 2 (6%–20%), 3 (21%–50%), 4 (51%–75%), 5 (76%–100%). Photomicrographs were taken with 35-mm Panatomic-X film (Eastman Kodak Co., Rochester, N.Y.).

Results

Physiologic variables measured after the anesthesic or control period in the three studies are listed in Table 1. Only Pao$_2$ values differed among experimental groups and in only the glucose utilization experiments.

Glucose Utilization Experiments

Electroencephalography. A sustained epileptiform pattern occurred in all rats in the high-dose alfentanil group and in none in the control group. Transient discharges occurred with the initial bolus dose of low-dose alfentanil (Figure 1A–D).

Autoradiography. Mean control values and percent change from control for CMRgl in brain regions with significant differences are listed in Table 2. In areas where change was observed, one of four patterns was identified: increased CMRgl after high-dose alfentanil; decreased CMRgl after high-dose alfentanil; increased CMRgl after low-dose alfentanil; or decreased CMRgl after low-dose alfentanil. In the hippocampal subregions, the primary area of interest of the study, CMRgl was significantly changed with high-dose alfentanil ($P = 0.03$; multivariate ANOVA). Subsequent analyses of these areas demonstrated increased CMRgl in the ventral hippocampus ($P = 0.0005$). In addition, increased CMRgl was evident in the lateral septal nucleus ($P = 0.0006$; univariate ANOVA). In the telencephalon and diencephalon, numerous areas of decreased CMRgl after high-dose alfentanil were present. In the telencephalon, this pattern occurred in the cortical areas, particularly the insular, piriform, and cingulate cortices and the caudate nucleus. In the diencephalon, this pattern occurred in most of the thalamic nuclei and the supraoptic and gelatinous nuclei. In the habenula, layers 4 and 5 of the cerebellum, and dorsal tegmental nucleus, increased CMRgl after low- but not high-dose alfentanil was apparent. In ventral, ventroposterior, and geniculate nuclei of the thalmus and in the gelatinous nucleus, decreased CMRgl occurred with low-dose alfentanil. There were differences ($P < 0.05$) between the high- and low-dose alfentanil groups in insular and pyriform cortices, caudate nucleus, lateral septal nucleus, ha-

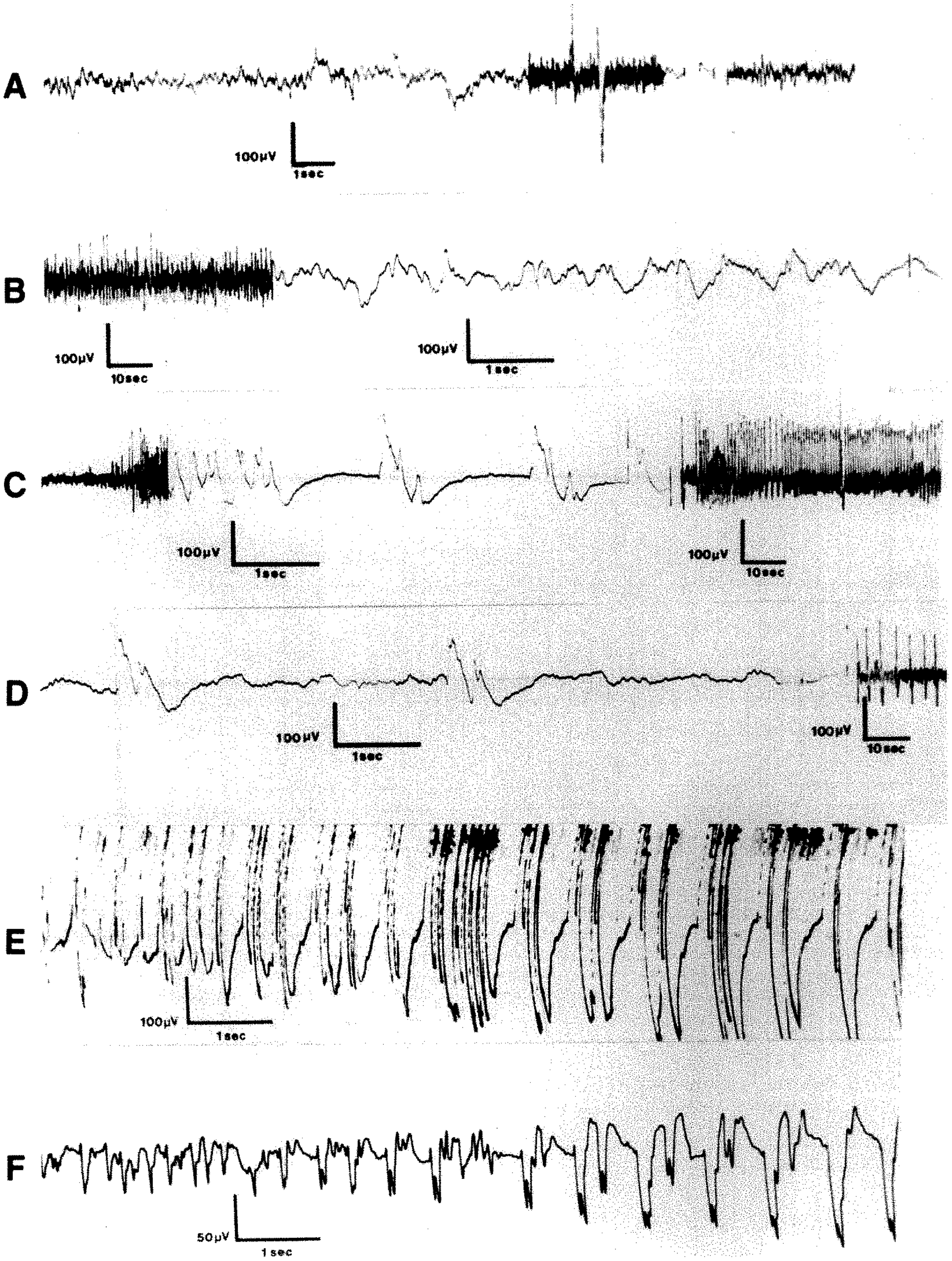

Figure 1. Subdermal biparietal and hippocampal EEG recordings of rats receiving either N_2O or alfentanil during paralysis and mechanical ventilation. **(A)** N_2O only; **(B)** low-dose group during maintenance infusion of alfentanil (15 $\mu g \cdot kg^{-1} \cdot min^{-1}$); **(C)** high-dose group after initial bolus dose of alfentanil (1000 μg/kg) (started immediately before EEG spikes and continued over 1–2 min); **(D)** high-dose group during maintenance infusion of alfentanil (100 $\mu g \cdot kg^{-1} \cdot min^{-1}$); **(E)** subdermal and **(F)** hippocampal EEG after intravenous injection of alfentanil (1000 μg/kg).

benula, supraoptic nucleus, ventroposterior and laterodorsal thalamic nuclei, dorsal lateral geniculate nucleus, and layer 4 of the cerebellum. Except for the lateral septal nucleus, in each case the CMRgl with low-dose alfentanil exceeded that with high-dose alfentanil.

Table 2. Cerebral Metabolic Rate for Glucose in Rats Anesthetized With Alfentanil[a]

	N_2O (control)	Alfentanil	Alfentanil group (% of N_2O control)	*P* value
Increased CMRgl After High-Dose Alfentanil				
Ventral hippocampus	78 ± 2	119 ± 3	152	0.0005
Lateral septal nucleus (64 ± 4)	79 ± 3	107 ± 4	135	0.0006
Decreased CMRgl After High-Dose Alfentanil				
Cortex				
Insular (75 ± 4)	110 ± 3	94 ± 3	85	0.02
Piriform (60 ± 3)	101 ± 5	81 ± 2	80	0.05
Cingulate (96 ± 3)	136 ± 3	124 ± 7	91	0.02
Caudate (77 ± 3)	110 ± 6	93 ± 1	85	0.02
Supraoptic nucleus	97 ± 4	75 ± 3	77	0.007
Thalamus				
Ventral (92 ± 3)	130 ± 8	97 ± 2	75	0.009
Ventroposterior	114 ± 4	91 ± 2	80	0.001
Mediodorsal	124 ± 6	101 ± 2	81	0.01
Laterodorsal	126 ± 6	96 ± 5	76	0.004
Medial geniculate (93 ± 3)	148 ± 3	109 ± 7	74	0.003
Lateral geniculate (90 ± 2)				
Dorsal	121 ± 5	87 ± 2	72	0.0007
Ventral	108 ± 4	84 ± 3	78	0.005
Gelatinous nucleus	123 ± 6	96 ± 4	78	0.02
Increased CMRgl After Low-Dose Alfentanil				
Habenula (90 ± 3)	134 ± 5	164 ± 7	122	0.0007
Dorsal tegmental nucleus	120 ± 8	147 ± 4	122	0.03
Cerebellum				
Layer 4 (95 ± 5)	108 ± 3	132 ± 5	122	0.03
Layer 5 (95 ± 5)	99 ± 4	122 ± 5	123	0.02
Decreased CMRgl After Low-Dose Alfentanil				
Thalamus				
Ventral (92 ± 3)	130 ± 8	109 ± 5	84	0.009
Ventroposterior	114 ± 4	104 ± 3	91	0.001
Medial geniculate (93 ± 3)	148 ± 3	122 ± 6	82	0.003
Lateral geniculate (90 ± 2)	121 ± 5	103 ± 4	85	0.0007
Gelatinous nucleus	123 ± 6	110 ± 4	89	0.02

[a] Cerebral metabolic rate for glucose (CMRgl) was measured in three groups of ventilated, paralyzed rats: N_2O (control), low-dose alfentanil, and high-dose alfentanil. Alfentanil CMRgl values listed are for high- or low-dose groups, as indicated in the left column; $n = 5$ in all groups. Only areas with $P < 0.05$ on univariate analysis of variance and subsequent least-significant difference testing versus N_2O-treated control rats are listed. Data are grouped as described in the text. Control and alfentanil values are reported as mean ± SEM, expressed in $\mu mol \cdot 100\ g^{-1} \cdot min^{-1}$. *P* values, univariate analysis of variance testing. CMRgl values from an earlier study in unstressed, unanesthetized rats using similar autoradiographic methods are in parentheses next to regions where such data are available (20).

Three-dimensional reconstruction of a series of representative autoradiograms (Figure 2) (12) shows many of these alfentanil-induced effects, including ventral hippocampal activation and thalamic depression of CMRgl after high-dose alfentanil.

Hippocampal Depth-Electrode Recordings

Electroencephalography. The control group showed no epileptiform activity in either subdermal or hippocampal EEG recordings. All rats given alfentanil exhibited epileptiform activity on both EEG recordings (Figure 1E and F).

Histologic Investigations

Electroencephalography. Subdermal electrodes indicated sustained epileptiform activity in all rats receiving alfentanil but in none of the control rats.

Histology. No microscopic lesions were observed in any of the 10 control brains examined. Evidence of acute neuronal degeneration on light microscopy was seen in 6 of 10 alfentanil-treated rats. The distribution of severity grades for the various foci is shown in Table 3. Neuronal degeneration was observed primarily in the limbic system and its areas of association. Two of the rats with lesions had minimal degeneration. In both of these, the lesions occurred in the dorsal amygdala adjacent to the lateral ventricle. Two others had mild to moderate degeneration. In one of these (rat 79), the lesions were found in the amygdala, the piriform cortex, and the ventral lateral septal nucelus. In the other (rat 73), a similar distribution of lesions was seen, but these were more severe and extended from the piriform cortex to the entorhinal cortex. Mild neuronal degeneration was observed in the anterior ventral cingulate cortex.

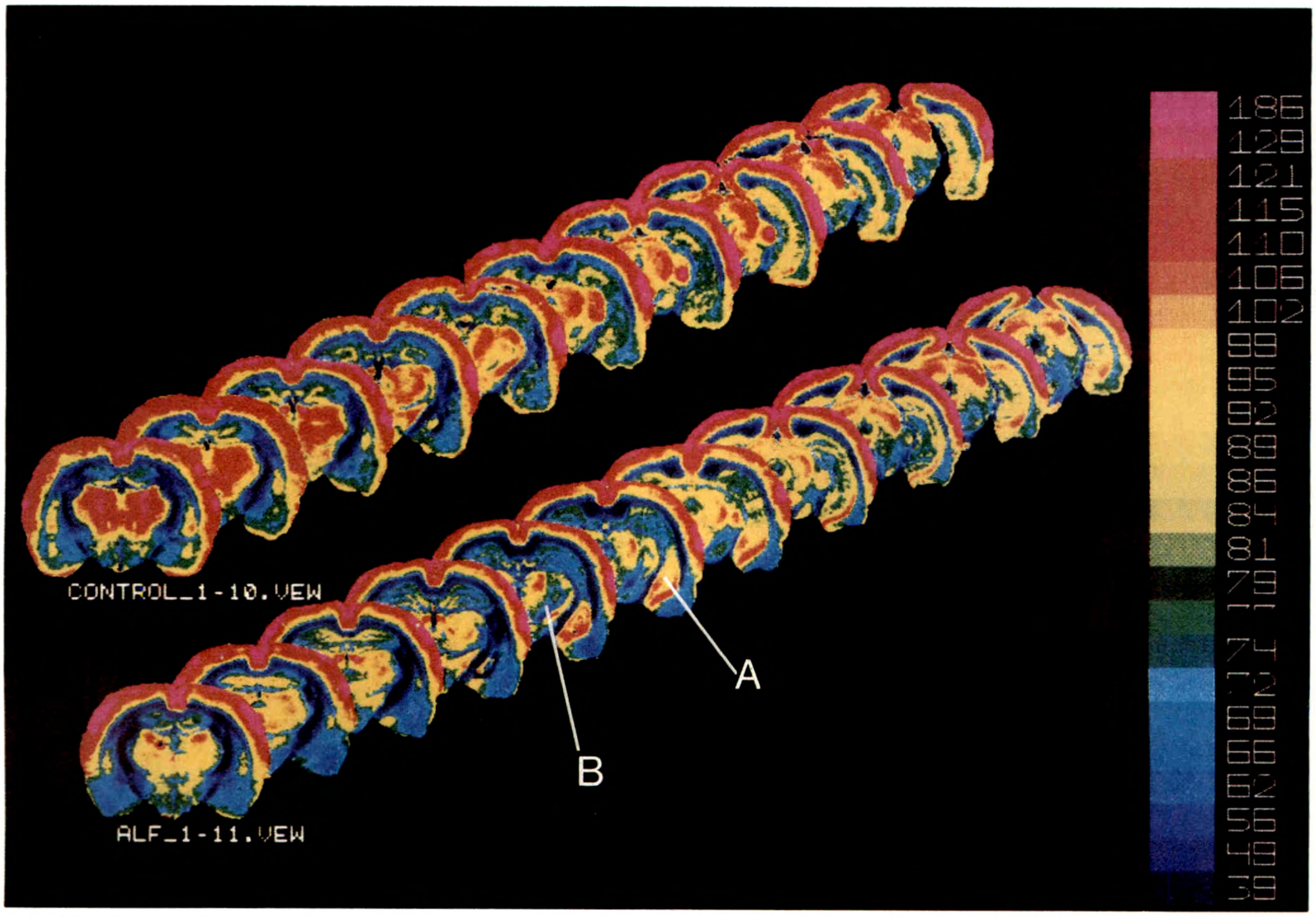

Figure 2. Computer-reconstructed images of CMRgl (μmol·100 g^{-1}·min^{-1}) in paralyzed, ventilated rats receiving either N_2O or high-dose alfentanil. Ventral hippocampal activation **(A)** and thalamic depression **(B)** are depicted. Images were made using computer programs written by L. S. Hibbard and J. S. McGlone (12).

Two of the 10 rats receiving high-dose alfentanil had moderate to severe neuronal degeneration that, as in the other rats, appeared only in the limbic system and its areas of association. The most consistently damaged regions were the amygdala, the adjacent piriform cortex, and the entorhinal cortex. The damage within the piriform cortex extended anteriorly to the level of the olfactory bulbs and involved the olfactory nuclei as well. The cingulate cortex, particularly the anterior and ventral portions, was also affected but less so than the piriform and entorhinal cortices. Multiple foci of neuronal degeneration were present within the pyramidal layer of the hippocampus, including at least some portions of CA1, CA2, CA3, CA4, and the subiculum. Within the thalamus, the most severely affected region was the medial dorsal area, although the medial middle and ventral portions of the thalamus and the dorsolateral thalamic area were also characterized by foci of acute degeneration. A moderate degree of degeneration was also evident within the ventral lateral septal nuclei of these two rats.

In all affected rats, areas of histopathology were characterized on low-power magnification (40×) by pallor and vacuolation of the neuropil (Figure 3), and on slightly higher magnification (100×) by perineuronal retraction spaces (Figures 4 and 5). On high-power magnification (430×), neurons with pyknotic nuclei and with retracted brightly staining eosinophilic cytoplasm could be seen (the characteristics of acute eosinophilic neuronal degeneration) (Figure 6). Some of the degenerating neurons within the pyramidal layer of the hippocampus were characterized by basophilic surface granules that may represent early mineralization of the cytoplasmic membrane or enhanced staining of terminal nerve boutons (Figure 7).

Discussion

In the present study in rats, doses of alfentanil that may be clinically relevant (i.e., 10- to 20-fold more than basal analgesic) produced limbic system hypermetabolism, epileptiform activity, and histologic evi-

Table 3. Distribution and Severity of Grades of Histopathologic Lesions in Alfentanil-Treated Rats[a]

	Animal No.					
Brain region	56	59	71	73	75	79
Olfactory nuclei	—	3	4	NE	—	—
Lateral septal nucleus, ventral	—	3	3	2	—	1
Amygdala	1	5	5	3	1	2
Cerebral cortex						
Cingulate	—	2	1	2	—	—
Piriform	—	4	5	4	—	2
Entorhinal	—	4	5	3	—	—
Hippocampus						
CA1	—	3	3	—	—	—
CA2	—	3	3	—	—	—
CA3	—	3	4	—	—	—
CA4	—	2	4	—	—	—
Subiculum	—	2	3	—	—	—
Thalamus						
Dorsomedial	—	4	5	3	—	—
Dorsolateral	—	2	3	—	—	—
Middle	—	4	2	—	—	—
Ventral	—	3	4	3	—	—

NE, not examined.

[a] Subjective scores of acute neuronal degeneration: — = none, 1 = minimal, 2 = mild, 3 = moderate, 4 = marked, and 5 = severe.

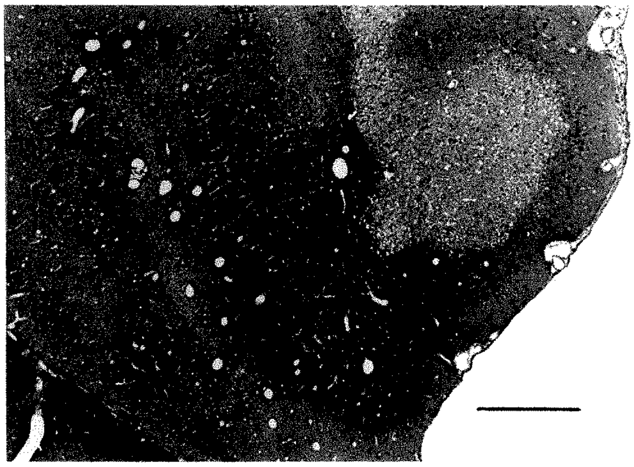

Figure 3. Amygdala, piriform cortex, and ventral hippocampus of alfentanil-treated rat 59. A prominent area of pallor (acute necrosis) is evident within the amygdala, and this extends to involve the piriform cortex (hematoxylin-eosin, original magnification, ×40; *bar* = 500 μm; dorsal aspect on left side of figure).

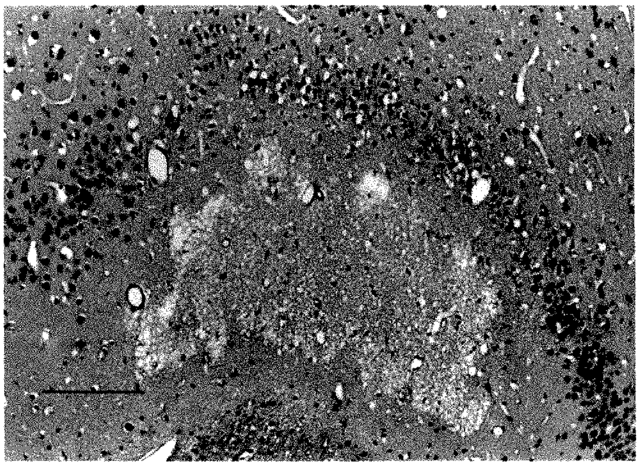

Figure 4. Piriform cortex adjacent to the lateral olfactory tract (*bottom*) of alfentanil-treated rat 73. A central area of pallor and vacuolation is present. Perineuronal retraction spaces are evident within the neuron layer of the piriform cortex, which is above this area of pallor (hematoxylin-eosin, original magnification, ×100; *bar* = 200 μm).

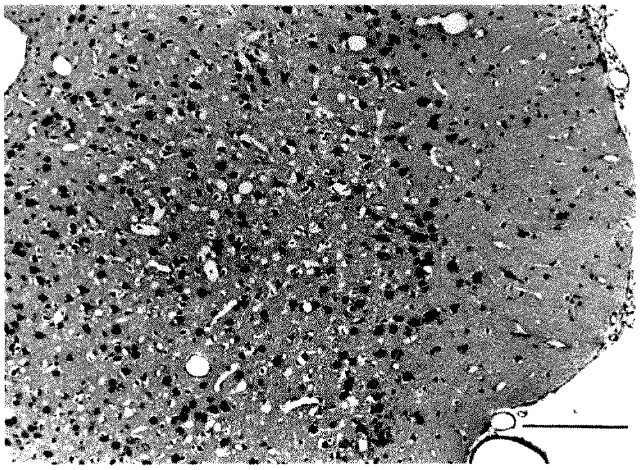

Figure 5. Anterior olfactory nucleus of alfentanil-treated rat 59. Marked, acute neuronal degeneration is evident, with prominent perineuronal retraction spaces (hematoxylin-eosin, original magnification, ×100; *bar* = 200 μm; dorsal aspect on left side of figure).

dence of brain injury. The metabolic and EEG effects of alfentanil are not surprising, because similar observations have been made with other μ-agonist opioids (1,2). Because intense, sustained seizures produce histologic evidence of brain damage (5,6,19), it was appropriate to use this rat model to assess the potential for damage produced by alfentanil-induced seizures. We believe that this is the first experimental evidence of histologic brain damage produced by a drug used in the clinical practice of anesthesia.

Methodologic Considerations

We used [6-^{14}C]glucose instead of a glucose analogue, such as deoxyglucose, as a tracer of CMRgl for the following technical reasons. The calculation of CMRgl using deoxyglucose requires the use of a factor (lumped constant) that can change with elevated CMRgl (10,11,20). Glucose requires no such constant. Exposure to [6-^{14}C]glucose, however, can result in loss of radiolabeled carbon in CO_2; therefore,

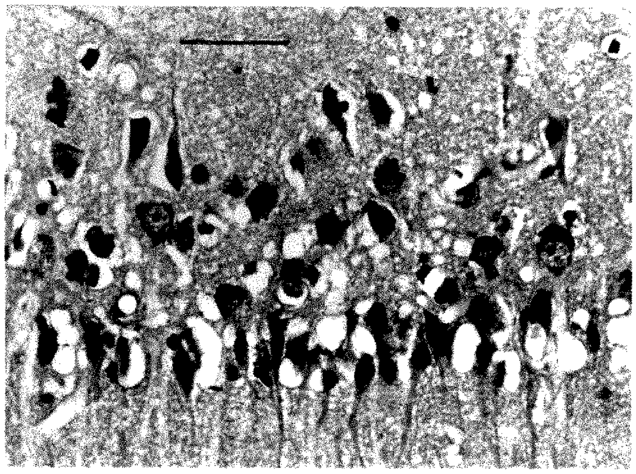

Figure 6. Pyramidal neuron layer of the hippocampus (CA1 region) of alfentanil-treated rat 59. Most neurons are undergoing acute degeneration, indicated by nuclear pyknosis, perineuronal retraction spaces, and prominently stained (eosinophilic) cytoplasm (hematoxylin-eosin, original magnification, ×430; *bar* = 50 μm).

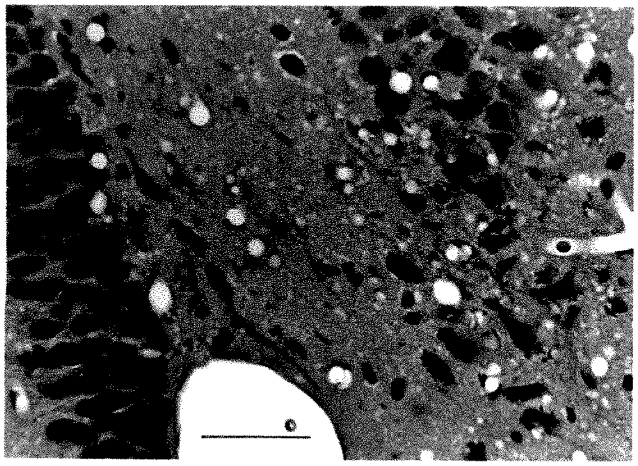

Figure 7. CA4 region of the hippocampus of alfentanil-treated rat 71. Acute neuronal degeneration involves the neurons in the pyramidal cell layer, present on the *right portion* of the photomicrograph. Some neurons, in addition to having pyknotic nuclei and eosinophilic cytoplasm, have small, surface basophilic "granules." These granules may represent foci of mineralization or enhanced staining of swollen or stretched terminal nerve boutons. A portion of the granule cell layer of the dentate gyrus is present at the *left margin* of the photomicrograph (hematoxylin-eosin, original magnification, ×430; *bar* = 50 μm; dorsal aspect on left side of figure).

the duration of exposure must be limited. Moreover, when a steady state is not present, autoradiography should be done as rapidly as possible. With the use of [6-^{14}C]glucose, autoradiographic procedures can be completed in 5 min rather than the 45 min necessary for the use of glucose analogues (20).

The influence of N_2O on glucose utilization in the control animals should be considered in the interpretation of these data. Comparison of the control CMRgl values with values obtained previously from unstressed, unanesthetized animals (20) (Table 2) suggests that N_2O sedation is associated with generalized, mild cerebral stimulation. This reinforces the conclusion that alfentanil induces hypermetabolism in some regions. Data suggesting no effect or metabolic depression in other regions, however, are more difficult to interpret.

Opioid-Induced Seizure Activity

Alfentanil administration after cessation of N_2O produced low-frequency, rhythmic, high-voltage spike activity, an epileptiform pattern (21,22), in subdermal recordings. This epileptiform pattern did not occur in the absence of alfentanil administration when N_2O was withdrawn in hyperoxic controls. Alfentanil also produced an epileptiform pattern when administered with N_2O. Thus, we conclude that the epileptiform pattern that we observed cannot be attributed to hyperoxia (17) or to N_2O withdrawal (18) and was induced by alfentanil. A possible hippocampal focus was suggested by the pattern of increased glucose utilization in the ventral hippocampus. Because depth electrodes were not used in the first experiments, we could not conclude with certainty that alfentanil produced hippocampal seizure activity (4). Thus, subsequent experiments were performed with recordings from depth electrodes placed in the hippocampus and with histologic investigation after overnight recovery.

Intracranial electrodes were placed in the dorsal hippocampus because of the regulatory role of this region on passage of paroxysmal activity into the entire hippocampus (16). This maximized the likelihood of detecting increased hippocampal activity. We observed seizure activity in these electrodes immediately after administration of a single injection of alfentanil, although after 1 h of alfentanil, hypermetabolism compared with N_2O-treated control rats was not apparent in the dorsal hippocampus but was present in the ventral hippocampus. Deoxyglucose autoradiography (which requires longer time) with sufentanil (2) and fentanyl (1) shows hypermetabolism of the entire hippocampus. These observations suggest that μ-opioid-induced seizure with concurrent hypermetabolism in these preparations occurs at temporally distinct times in different areas of the hippocampus.

Other studies have found conflicting evidence of both proconvulsant and anticonvulsant properties specific to opiate-receptor agonists. Snead and Bearden (4) used depth EEG electrodes and injected various doses of μ-, δ-, κ-, ϵ-, and σ-opiate-receptor agonists into the cerebral ventricles of rats. They reported proconvulsant properties of all five classes of agents with descending potency $\epsilon > \delta > \mu > \sigma >> \kappa$. Distinct EEG patterns occurred with each opiate subtype. The μ-opiate-induced seizures originated in the subcortex and the hippocampus and then generalized. Other published data provide evidence that fentanyl and its congeners are μ-agonists (23–26) and that nonopioid seizures are generally associated with hypermetabolism (5,6,27). These data, added to our findings of limbic system hypermetabolism, EEG epileptiform patterns, and neuronal lesions after high doses of alfentanil, lead us to conclude that opioid-induced seizures occurred in the limbic systems in our rats.

Opiatergic Systems

Increased glucose utilization occurred in the ventral hippocampus after high-dose alfentanil. This is consistent with observations of the effects of other opioids (1–3,28). Chugani et al. (3) observed effects with enkephalin similar to our findings: increased ventral hippocampal and lateral septal metabolic rate with depression of most thalamic structures and the piriform cortex. Tommasino et al. (1), with higher doses of fentanyl administered in rats, observed decreased thalamic CMRgl and increased ventral hippocampal CMRgl (compared with values in unanesthetized controls), although they noted little change in the septal nucleus and decreased CMRgl in the habenula. They also noted decreased CMRgl in numerous other areas not observed by us. Young et al. (2), in rats given sufentanil, also observed increased hippocampal CMRgl involving the ventral hippocampus and decreased thalamic CMRgl (compared with values in N_2O-sedated controls). Thus, autoradiographic measurements of CMRgl suggest a distribution of μ-receptors in rats associated with metabolic stimulation in the ventral hippocampus and depression in the thalamus. However, the presence of thalamic lesions in 3 of our 10 alfentanil-treated rats implies that thalamic metabolic depression could have resulted from injury rather than through a specific receptor-mediated mechanism.

Hippocampal GABAergic interneurons are known to exert inhibitory control over pyramidal cells. These interneurons are inhibited by a μ-receptor agonist (29) and are activated (made more inhibitory) by peptidergic afferents arising in the amygdala (30). Thus, one reasonable cellular mechanism can be posited for the observed hippocampal excitatory effects of μ-agonist opioids (i.e., direct inhibition of hippocampal interneurons) and injury-induced loss of amygdala-mediated inhibition.

Opioid-Induced Brain Damage

Data from a variety of models and species support the thesis that seizures without hypoxia can permanently damage neural tissue (5,6,19,31,32). Lothman and Collins (5) and Ben-Ari et al. (6) observed a qualitative correlation between regional increases in glucose utilization produced by kainic acid, pentylenetetrazole, or bicuculline and regional neuropathologic changes. Our data demonstrate a similar phenomenon with alfentanil. That is, hypermetabolic areas such as the hippocampus and lateral septal nucleus are prone to alfentanil-induced damage. However, our rats with high-dose alfentanil had only a 5-min exposure to radiolabeled glucose after 1 h of epileptiform activity. Thus, areas of the brain that had already been injured would exhibit decreased CMRgl, whereas areas that were still functional could exhibit hypermetabolism. It is not surprising, therefore, that the pattern of neuropathology that we observed is not precisely congruent with the autoradiographic pattern of hypermetabolism. Nevertheless, our data are consistent with the conclusion that alfentanil in doses sufficient to produce regional epileptiform activity and hypermetabolism in rats can produce neuronal lesions.

The autoradiography experiments were performed first. We chose to test alfentanil because it was a recently released fentanyl analogue with unknown effects on regional CMRgl. The doses chosen were intended to model clinical practice. Published data indicated that the low dose we chose was moderately analgesic and sedative in rats (8). Thus, we set our high dose at 10- to 20-fold greater, modeling clinical recommendations for high-dose anesthetic opioid techniques (Janssen Pharmaceuticals. Sublimaze and Sufenta product information. Physician's desk reference. Oradell, N.J.: Medical Economics, 1990: 1089–92). This was done empirically, fully cognizant that rodent and human dose-response relationships may not necessarily be parallel. In previous studies (19), we found that seizure activity in rats occasionally caused a decrease in Pa_{O_2}. Thus, we elected to use 100% O_2 in alfentanil-treated animals, although this does raise the issue of whether N_2O withdrawal (18) and hyperoxia (17) contributed to the observed seizure activity or brain damage. These two issues were addressed in the design for the subsequent hippocampal depth-electrode recordings and histologic investigations. The data suggest that neither N_2O withdrawal nor hyperoxia contributed to the alfentanil-induced epileptiform activity or to resultant brain damage. Finally, in the histologic studies, the alfentanil loading dose was further doubled with moderate hypocapnia to maximize the likelihood of brain damage. Clearly, further studies are needed to ascertain the dose-response relationship among alfentanil administration, seizures, and brain damage.

Not every rat receiving a high dose of opioid in our study sustained brain damage. Other clinically relevant factors, such as genetic predisposition, Paco_2, or cerebral perfusion pressure, may have contributed to the development of brain injury in the affected rats. Of note, fentanyl in rats has been reported to exacerbate cerebral ischemic injury (33). Thus, one might speculate that if opioid-induced seizure activity coincides with a low cerebral blood flow situation, the risk of ischemia-induced neural injury may be increased.

We have demonstrated that an opioid, in the circumstances described, can be a neurotoxin. Several lines of evidence support the notion that opioids have the potential to be neurotoxic in rodents in an excitotoxic manner analogous to that reported with kainic acid (5,6,31,34) and domoic acid (35–37):

1. Both kainic acid (31,34) and alfentanil produce hippocampal seizure on EEG recordings from intracranial electrodes.
2. Autoradiographic studies with deoxyglucose of kainic acid (5,31) and opioids (1,2) reveal a striking similarity in the pattern of hypermetabolism.
3. The pattern of brain damage in rodents produced by domoic acid (35–37) is very similar to that produced by alfentanil in our most severely affected rats and by kainic acid. Domoic acid is a structural and functional analogue of kainic acid (34).
4. In rodents, limbic system seizure produces a stereotypic behavior, "wet dog" shakes. This behavior can be produced with domoic acid (35), kainic acid (31), and μ-agonist opioids (38). Kainic acid-induced wet dog shakes are potentiated by μ-agonists in a naloxone-reversible manner (39). Indeed, there are reports that this stereotypic manifestation of limbic seizure in rats is mediated by endogenous μ-agonist peptides (40).
5. Kainic acid and domoic acid are both thought to be neurotoxic via excitatory mechanisms (34) involving activation of glutamate receptors (41–43). Opioids have been reported to also activate glutamate channels (44–46).

These observations might ordinarily be considered nothing more than interesting laboratory phenomena. However, domoic acid has been ingested inadvertently by humans (47,48), producing lesions comparable to those seen in domoic acid-treated and alfentanil-treated rats. Victims exhibited neurologic symptoms including seizures and coma, had permanent memory deficits (47), and sustained large, delayed decrements in CMRgl in the hippocampus and amygdala on positron emission tomography (47). Neuropathologic evaluation in victims who died (47) and in monkeys under controlled conditions (49) also revealed limbic system (hippocampus and amygdala) damage.

Although debated for several years (50–52), recent reports document that exogenously administered opioids can produce brief epileptiform activity on EEG recordings in humans (53,54) and that endogenous opioids may contribute to seizures in some epileptic humans (55,56). However, the usual prerequisite for seizure-induced brain damage, prolonged and intense seizure activity, has not been reported in humans given opioids. Thus, the potential for opioids to be neurotoxic in humans at this point must be considered highly speculative.

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Time-Course of Respiratory Depression After an Alfentanil Infusion-Based Anesthetic

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Postoperative respiratory depression after alfentanil administration has been described in several case reports. The effects of a prolonged alfentanil infusion on the CO_2 response curve or cognitive function have not been studied. Twenty-one ASA physical status I or II patients were studied after a prolonged alfentanil infusion (>90 min) to determine the incidence of postoperative respiratory depression, arterial O_2 desaturation, and impairment of cognitive function. Each patient's recovery was observed at 30-min intervals for evidence of respiratory depression (utilizing the Read CO_2 rebreathing method), desaturation by pulse oximetry (severe desaturation defined as arterial O_2 saturation <90%), and cognitive function (utilizing Trieger dot and digit substitution tests). Plasma samples were also examined for secondary elevations in alfentanil plasma concentrations. Significant depression of the CO_2 response curve and cognitive function was found up to 1 h postoperatively. Arterial O_2 desaturation was seen in 11 of 21 patients (52%). No correlation was found between arterial O_2 desaturation and cognitive function scores or CO_2 rebreathing results. Increased depression of the CO_2 response curve was not necessarily associated with severe desaturation episodes. A secondary increase in plasma alfentanil concentration was detected in 5 of the 21 patients (24%), but these patients did not experience further depression of the CO_2 response curve. We conclude that prolonged alfentanil administration may result in severe arterial O_2 desaturation with significant depression of the hypercapnic respiratory drive during the first hour in the postanesthesia care unit, even though the majority of our patients were easily aroused in response to verbal stimuli.

(Anesth Analg 1992;75:965–71)

Postoperative respiratory depression is a recognized complication after opioid anesthesia. Fentanyl, a relatively short-acting opioid, causes respiratory depression that may be associated with a secondary peak in plasma fentanyl concentration (1,2). The time-course of this respiratory depression can be an important factor in governing postoperative risks and recovery room stay. Alfentanil, a short-acting fentanyl analogue, might have an advantage over other opioids if it leads to a more rapid return to normal consciousness and respiration (3–5). There is, however, the potential for prolonged recovery when the duration of administration of alfentanil is extended. Recently, several case reports have described delayed postoperative respiratory depression after alfentanil infusion (6–8). The purpose of this study was to determine the extent and time-course of respiratory depression, as well as the recovery of consciousness, after alfentanil/N_2O/O_2 anesthesia in procedures lasting longer than 90 min.

Methods

Twenty-one ASA physical status I or II patients scheduled for elective lumbar discectomy gave written, informed consent to participate in this protocol approved by our institutional review board. Patients were excluded from the study according to the following criteria: history of pulmonary disease, CO_2 retention, obesity (weight >110 kg), athletes in training, pregnancy, allergy to opioids, substance abuse, or renal failure.

Instrumentation and Data Collection Procedures

Respiratory data were collected using a Medical Graphics System 2001 (Medical Graphics Corpora-

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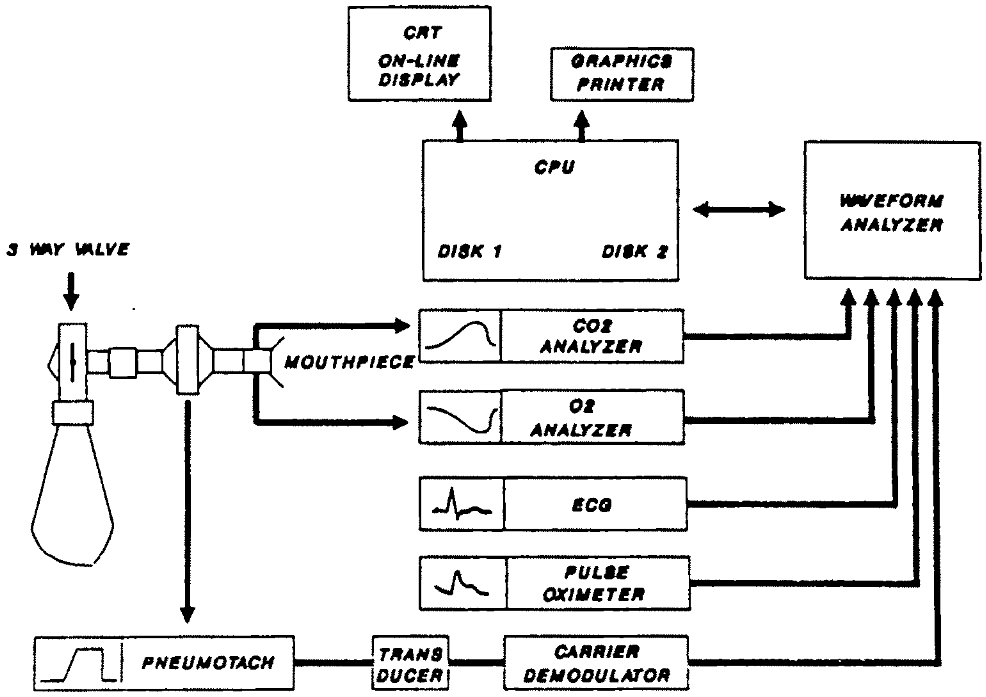

Figure 1. Schematic of the computerized CO_2 modified Read breathing flow circuit. CRT, cathode-ray tube; CPU, central processing unit; ECG, electrocardiogram.

tion, St. Paul, Minn.) (Figure 1). Oxygen and CO_2 gas analyses were performed with Sensors (Dynatec Electro-optics, San Luis Obispo, Calif.) rapid analyzers requiring a total of 150 mL of gas sample per minute. The O_2 analyzer operates with a zirconia fuel cell sensor heated to maintain a temperature of 75°C. The analyzer has a linearity range of 0%–100% O_2, with an accuracy of ±0.05% O_2 or 1% of the reading, whichever is smaller.

The CO_2 analyzer is an infrared absorption type with a linearity range of 0%–10% CO_2 and an accuracy of ±0.2% at full scale. Both analyzers have a response time of <100 ms. The analyzers were calibrated with certified gas mixtures of 16% O_2 and 7% CO_2 (Puritan Bennett, Baltimore, Md.), accurate to ±0.03%.

Flow was measured with a heated linear pneumotach (Hans Rudolph model 3813), with a flow range specification of 0–800 L/min. The pneumotach was calibrated using a 3-L calibration syringe. Five injections of room air were performed with an average error not >1.5% of injected volume.

The rebreathing circuit resistance was 0.5 cm H_2O at a flow rate of 1 L/s. Gas and flow signals were processed by an eight-channel microcomputer for real-time data. Phase delays from gas transport time and from body temperature, pressure, saturated volume corrections were applied for every breath. The processed data were written onto the computer hard disk and instantly displayed on the screen.

A complete system calibration (analyzers, pneumotach, and phase delays) was performed before each CO_2 response test.

Testing Procedures

Each patient was transported to the postanesthesia care unit (PACU) on a hospital stretcher approximately 1.5 h before the scheduled surgery. The patient was positioned supine in a semirecumbent position, and once comfortably resting on the stretcher, he or she was familiarized with the cognitive function tests (Trieger dot [9] and digit substitution [10]), a linear analogue pain scale, and the respiratory apparatus used for the CO_2 response measurements. A 15-min relaxation period was allowed before performing each baseline test. During that period, the rebreathing bag (13 L) was flushed three times with the rebreathing gas mixture (93% O_2, 7% CO_2). The bag was filled with a volume equal to the patient's predicted vital capacity plus 1 L via a 9-L water seal spirometer (Warren E. Collins Inc., Braintree, Mass.). The cognitive function tests and pain assessment scale were performed first, followed by the rebreathing test. This test was performed with the patient breathing through a large mouthpiece and wearing noseclips. These tests were performed over a 15-min period preoperatively and postoperatively. On completion of all baseline tests, an arterial catheter was inserted into the radial artery to facilitate

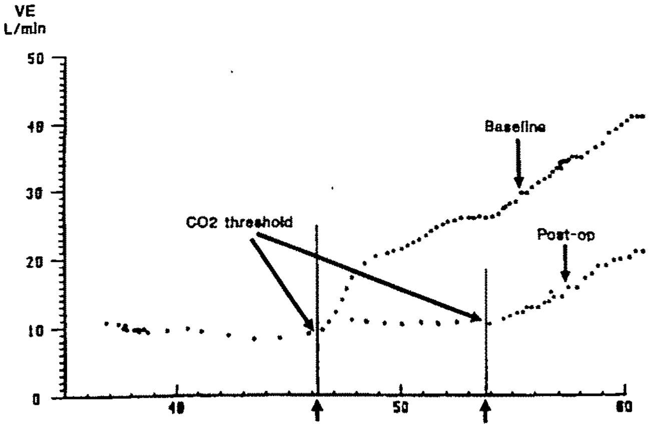

Figure 2. Representative CO_2 response curves from one patient. Each *dot* represents a single breath.

serial blood collection for determination of alfentanil plasma levels. The first postoperative test was performed once the patient was awake and responsive to verbal commands.

Evaluation of the CO_2 Response Curve

The CO_2 response was analyzed after each test from the corresponding breath-by-breath computer graph. Swallowing and coughing were recognized by a computer algorithm and excluded during the performance of the test. The slope of the CO_2 response curve was determined for the linear portion of the curve, beginning at the CO_2 "threshold" (11,12) (Figure 2), which was visually identified as the point at which ventilation began to increase linearly with increasing CO_2. The corresponding end-tidal Pco_2 ($P_{ET}co_2$) value was selected from the x-axis and entered into the computer for subsequent calculation of the slope, beginning at the "threshold" value.

The slope of the CO_2 response was computed via linear regression analysis by the method of least squares. The correlation coefficient (r) and coefficient of determination (r^2) were calculated for each line. We selected the breath-by-breath technique for this evaluation, because it has been reported to be more powerful than segmental-time averaging in this application (13). The slope estimation thus obtained yields the highest statistical confidence. This is particularly important when only a single trial is available for each experimental state. This approach therefore minimizes the chance of missing a real empirical difference and provides the narrowest confidence limits for each estimate (14).

Anesthetic Technique and Postoperative Data Collection

Premedication consisted of either intravenous midazolam (2–4 mg), administered 10 min before induction, or oral diazepam (5–10 mg), administered 30 min before induction. After breathing O_2 for several minutes, anesthesia was induced using pancuronium (0.015 mg/kg IV), alfentanil (75 μg/kg IV) over 90 s, and thiopental (1–4 mg/kg). Succinylcholine (1.5 mg/kg IV) was utilized to facilitate endotracheal intubation.

Anesthesia was maintained with 60%–70% N_2O in O_2 and an alfentanil infusion (1.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$) that was adjusted in increments of 0.25–0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in response to a change in arterial blood pressure or heart rate of 10% or greater, or both, as clinically indicated (e.g., arterial blood pressure, heart rate, and sympathetic signs). Neuromuscular blockade was achieved by administration of pancuronium that was titrated to maintain a twitch response of 2/4 utilizing a peripheral nerve stimulator. Neuromuscular blockade was reversed with neostigmine (2.5 mg) and atropine (1 mg) intravenously. The alfentanil infusion was discontinued 20–30 min before the anticipated end of surgery. Nitrous oxide was discontinued on completion of skin closure.

Every patient was breathing O_2 by mask on admission to the PACU. Once the patients were awake, stable, and appeared to be breathing well, O_2 administration was discontinued. If arterial O_2 desaturation occurred (arterial O_2 saturation [Spo_2] <95%), the patients were given supplemental O_2 until their Spo_2 returned to 95% or more. Postoperative measurements (Trieger dot, digit substitution, rebreathing tests, and the visual analogue pain assessment) were started within the first 30 min after arrival in the PACU, once the patient became alert and cooperative. The measurements were continued at approximately 30-min intervals until pain medication was requested or the patient was discharged from the PACU. A final measurement was obtained at 120, 150, or 180 min postoperatively, depending on when the patient received supplemental pain medication or was discharged from the PACU. The actual discharge time varied from patient to patient but reflected the time to awakening when each patient could maintain an Spo_2 >95% on room air. These final data were combined into one time point and labeled "last." Blood specimens were obtained from the arterial catheter for determination of alfentanil plasma levels. Alfentanil levels were determined by a radioimmunoassay (15) that uses rabbit antialfentanil antibodies and has a sensitivity of 0.1 mg/mL and an interassay and intraassay coefficient of variation that is <5%. The CO_2 response curve was immediately plotted

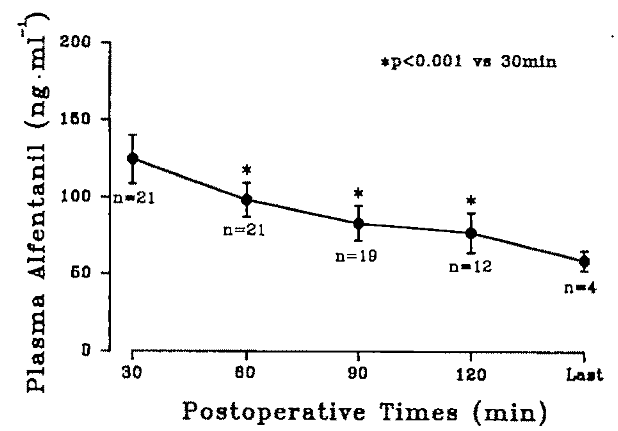

Figure 3. Mean ± SEM plasma alfentanil levels obtained at 30, 60, 90, 120, and 150 (Last) min postoperatively.

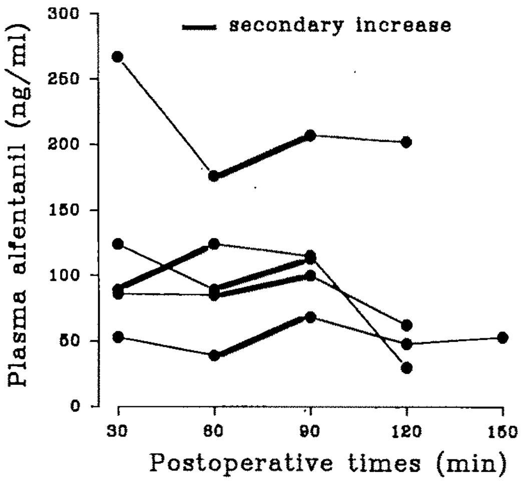

Figure 4. Alfentanil plasma concentrations in the five patients with a secondary postoperative elevation in alfentanil level.

from the simultaneous breath-by-breath minute ventilation and P_{ETCO_2} values. The two measures of respiratory drive, described earlier, were then calculated: the slope of the ventilation versus P_{ETCO_2} curve and right displacement of the curve. Incidences of arterial O_2 desaturation were defined as moderate (Sp_{O_2} 90%–95%) and severe (Sp_{O_2} <90%) while the patient was breathing room air. The Sp_{O_2} measurements were recorded only when the pulse oximeter reading was consistent over a 5-min observation period. When arterial O_2 desaturation was rapid and severe (Sp_{O_2} <80%), the patient was given O_2 to breathe for a 5-min period after which a second reading was obtained with room air to ensure against artifact errors. Changes in the CO_2 response curves, plasma alfentanil levels, and Trieger dot and digit substitution tests were analyzed using analysis of variance for repeated measures, with $P < 0.05$ considered statistically significant. A protected least-significant difference test was used to identify differences between means. A Pearson correlation matrix was used to determine whether there were relationships among alfentanil plasma levels and respiratory and cognitive function variables. The Bartlett χ^2 statistic was used to determine significance. All values are presented as mean ± SEM.

Results

The average age of the patients was 36 ± 1.6 yr, and mean surgical time was 186 ± 6.5 min (range 120–240). The average alfentanil dose of 18.9 ± 1.6 mg (range 10.7–38.5) yielded postoperative plasma alfentanil levels ranging from 124.5 ± 15.6 ng/mL to 58.9 ± 6.4 ng/mL (Figure 3). Alfentanil concentration decreased significantly ($P < 0.001$) for the first 120 min. Statistical significance was not achieved ($P = 0.114$) when including the 150-min time point as a result of the smaller n value ($n = 4$). Five of 21 (24%) patients demonstrated a secondary increase in plasma alfentanil concentration postoperatively (Figure 4). A significant correlation ($r^2 = 0.84$) was found between alfentanil plasma levels and the percent change from baseline to 30 min postoperatively in the CO_2 response curve. No significant correlations were found between plasma alfentanil levels and the change in the CO_2 response curve from baseline to each of the other three postoperative time points. There were also no significant correlations between plasma alfentanil and Sp_{O_2} at any of the measurement periods in those patients. The mean coefficient of determination r^2 for the CO_2 responses was 0.95, and there were no significant differences between r values at each measurement period. The mean CO_2 response slopes were depressed 40%, 28%, 19%, and 17% from baseline at 30, 60, 90 min, and the last measurement, respectively ($P < 0.001$) (Figure 5). Further evidence of respiratory depression was indicated by a significant increase ($P < 0.05$) in right displacement of the CO_2 response curve during the postoperative period compared with baseline. The mean CO_2 threshold increased significantly ($P < 0.001$) from 46 ± 0.70 mm Hg at baseline to 50 ± 0.72, 50 ± 0.73, 51 ± 0.73, and 49 ± 0.70 mm Hg at 30, 60, 90 min, and the last measurement, respectively.

Eleven of 21 patients (52%) experienced desaturation (Sp_{O_2} <95%) during the first postoperative hour. Eight of 21 patients (38%) demonstrated severe desaturation (Sp_{O_2} <90%). The latter required intervention by an investigator in the PACU to arouse the patient to take deep breaths. The patients who experienced severe postoperative desaturation did not necessarily have the highest alfentanil plasma concentration nor evidence of a secondary increase in plasma alfentanil (Table 1).

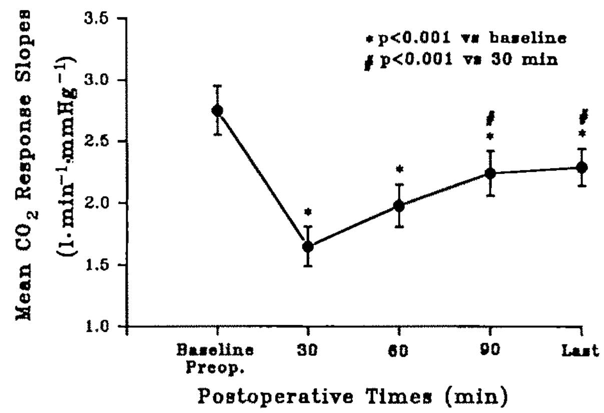

Figure 5. Mean ± SEM CO_2 response slopes measured preoperatively and at 30, 60, and 90 min postoperatively. Last, measurement taken before PACU discharge at 120, 150, or 180 min.

We compared the percent change from baseline in the CO_2 response curves in patients experiencing severe postoperative arterial O_2 desaturation with those who did not experience desaturation and found no significant difference between the two subgroups. In the eight patients who experienced severe postoperative desaturation, we found nonsignificant correlations (r^2 = 0.13, 0.47, 0.19) between postoperative respiratory depression, quantitated by the percent change from baseline in the CO_2 response curve, and postoperative desaturation measured by pulse oximetry at 30, 60, and 90 min, respectively. By 120 min postoperatively, 19 of the 21 patients had Spo_2 >97%. Two patients continued to show lower Spo_2 (93% and 94%), but these values returned to normal at 150 min. Only at 30 min postoperatively was there a significant correlation (r^2 = 0.58) between plasma alfentanil and Spo_2 in those eight patients.

Digit substitution and Trieger dot tests were significantly lower at all postoperative times compared with baseline (Figures 6 and 7). Impaired cognitive function was greater during the initial 30 min, with return to baseline by 120 min. All patients performed significantly below their baseline on the digit substitution and Trieger dot tests for the first 120 min of their postoperative stay in the PACU. Episodes of severe desaturation were not associated with lower scores on the digit substitution or Trieger dot tests compared with patients with normal Spo_2. The percent change from baseline in that subset of patient scores was not significantly different between those two groups.

Pain scores, as determined by a linear analogue pain scale, were significantly higher than baseline throughout the postoperative period. At the final assessment, they were significantly increased above all other times (Figure 8).

Discussion

Respiratory depression after fentanyl administration may be associated with a secondary increase in plasma concentration (1,2). Stoeckel et al. (1) and Becker et al. (2) demonstrated delayed respiratory depression after fentanyl administration. Owing to its short elimination half-life, the alfentanil plasma concentration might be expected to decrease steadily, avoiding the secondary peaks in plasma concentration and possible respiratory depression. Three recent reports have described delayed respiratory depression after an alfentanil infusion (6–8). In these reports, alfentanil was titrated clinically to effect. These studies, however, did not consistently examine CO_2 response curves, cognitive recovery, or alfentanil plasma concentrations.

In this study, we found statistically significant depression of the CO_2 response curve for 120 min postoperatively (Figure 5). This was accompanied by a significant right shift of the slope. Accurate measurement of ventilation was made possible by the real-time integration and processing of CO_2, O_2, and flow waveforms under the dynamic conditions of a CO_2 Read rebreathing challenge. Using this technology, we were able to clearly demonstrate that on average, P_{ETCO_2} had to increase to 50 mm Hg to provoke a ventilatory response. Furthermore, we found that 52% of our patients had an Spo_2 <95%. Often desaturation occurred when the patients fell asleep, even though they appeared awake and alert immediately before these episodes while tests were being performed. This is consistent with the effects of sleep on the CO_2 response curve, as reported by Belville et al. (16), as well as the combination of opioid potentiation and sleep on the depression of the CO_2 response curve (17).

In their study of respiratory depression with alfentanil, Mahla et al. (6) obtained a single plasma sample to determine the concentration of alfentanil at the time of the respiratory depression (45 min after discontinuation of alfentanil) and reported a mean of 87 ng/mL. Their postoperative alfentanil plasma concentrations at 30 min (±10 min) ranged from 40 to 289 ng/mL. These concentrations are in the range reported by Ausems et al. (18) at which spontaneous ventilation resumes (99–223 ng/mL). Only two of our study patients exceeded that range. We observed a secondary increase in plasma alfentanil concentration in 24% of the patients studied. Because we did not find a consistent correlation between alfentanil plasma concentration and the CO_2 response curve or arterial O_2 desaturation (Spo_2 <90%) in the patients who demonstrated a secondary increase, we could not attribute arterial O_2 desaturation or depression of the CO_2 response curve to this mechanism.

It is possible that the duration and degree of respiratory depression reported in this study were affected

Table 1. Arterial O_2 Saturation, Alfentanil Plasma Levels, and CO_2 Response Changes From Baseline in Eight Patients Who Experienced Severe Postoperative Arterial O_2 Desaturation

	Patient No.							
	1	2	3	4	5	6	7	8
Preoperative (baseline)								
Plasma alfentanil (ng/mL)	0	0	0	0	0	0	0	0
SpO_2 (%)	100	100	100	100	100	100	100	100
Postoperative								
30 Min								
Plasma alfentanil (ng/mL)	52.7	127.9	124.2	267.0	288.9	70.8	196.2	184.2
Spo_2 (%)	75	77	88	89	90	76	79	89
CO_2 response (% from baseline)	−4.0	−40.5	−41.0	−86.0	−42.5	−22.0	−55.0	−9.0
60 Min								
Plasma alfentanil (ng/mL)	39.4	115.1	89.3	176.4	192.4	66.0	175.9	139.6
Spo_2 (%)	80	79	97	90	100	95	95	94
CO_2 response (% from baseline)	−53.5	−51.0	−35.0	−59.5	−2.5	−22.0	−0.5	10.5
90 Min								
Plasma alfentanil (ng/mL)	68.3	101.4	112.7	206.7	154.0	53.1	150.6	110.1
Spo_2 (%)	95	90	97	100	100	100	100	94
CO_2 response (% from baseline)	0.0	2.0	−20.5	−66.5	−2.5	−20.0	−4.0	−12.0

Spo_2, arterial O_2 saturation.

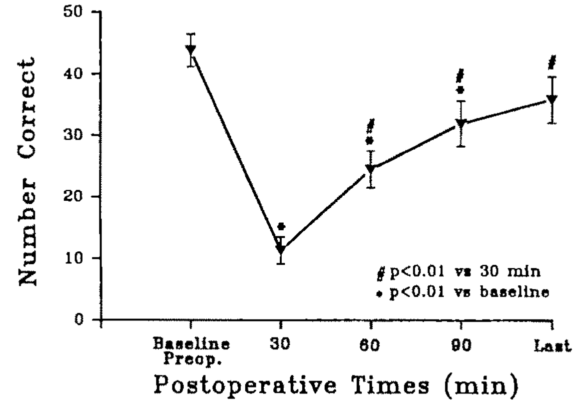

Figure 6. Digit substitution tests expressed as mean ± SEM number of correct answers. Last, measurement taken before PACU discharge at 120, 150, or 180 min.

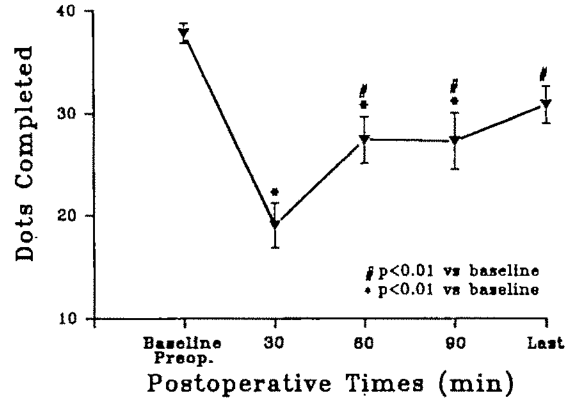

Figure 7. Mean ± SEM Trieger dot test scores expressed as the number of completed dots. Last, measurement taken before PACU discharge at 120, 150, or 180 min.

by the interaction of diazepam, midazolam, or thiopental with alfentanil. Our study was designed to examine the effect of an alfentanil-based infusion on ventilation and recovery when used in a clinical setting. Bailey et al. (19) have shown that the combined use of fentanyl and midazolam for sedation resulted in a 92% incidence of hypoxemia and apnea and 50% with fentanyl alone. Obviously, the hypoxic drive to ventilation may be depressed further by the addition of midazolam to our alfentanil-based technique.

Other studies have demonstrated that benzodiazepines can cause depression of the CO_2 response curve; however, the clinical significance of these effects has been questioned (20–23). Power et al. (23) examined the CO_2 response curve in seven healthy volunteers receiving either intravenous diazepam (0.15 mg/kg) or midazolam (0.075 mg/kg), and found that both drugs resulted in transient nonsignificant depression in the slope of the CO_2 response curve in their subjects. Bailey et al. (22) demonstrated that 0.1 mg/kg of diazepam, as an intravenous bolus dose, did not cause significant depression of the ventilatory response to CO_2. These and other studies (20,21) suggest that the clinical effects of the benzodiazepines, administered at the time of induction, can be expected to be short-lived. The duration of surgery averaged 2–3 h, and tests were performed up to 3 h postoperatively. In this study, we found that the CO_2 response slopes were significantly depressed from control values over all measured time periods. Although the benzodiazepines did not have a direct respiratory effect, it is possible that their residual sedative effects, coupled with those of thiopental, may have led to more sleep episodes, which are

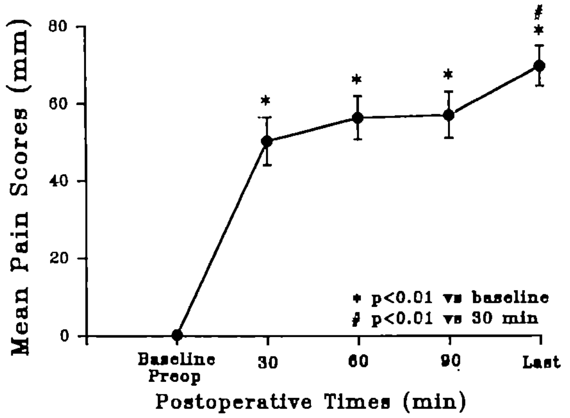

Figure 8. Mean ± SEM pain scores (min) measured on a 10-cm linear analogue scale. Last, measurement taken before PACU discharge at 120, 150, or 180 min.

known to enhance respiratory depression (16,17). The episodes of desaturation observed in this study most often occurred when the patients were asleep but arousable to verbal stimuli.

Postoperatively, the ventilatory response to CO_2 in our patients was depressed to a greater extent at 30 and 60 min postoperatively despite increasing pain scores on the visual analogue pain scale (Figures 5 and 8). Pain scores were highest at the last measurement, whereas the respiratory response to CO_2 did not further improve compared with the 90-min measurement.

Postoperative respiratory depression is a problem that can occur after administration of any opioid. The alfentanil pharmacokinetic profile (shorter elimination half-life and more rapid clearance) may limit this problem. The depressed CO_2 response and arterial O_2 desaturation reported here are of concern, particularly during the first hour in the PACU. The effects were reversed with stimulation and encouragement to breathe. Clinical observation alone did not predict these events. A secondary increase in plasma alfentanil concentration did occur in some of our patients; however, this did not seem to influence respiration. Of note, formal cognitive testing around the time of the desaturation episodes showed no relationship between patients who had arterial O_2 desaturation and those who did not. This confirmed our observations that patients who had arterial O_2 desaturation often appeared as alert and awake as others who did not.

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R-Phenylisopropyl-Adenosine Increases Spinal Cord Blood Flow After Intrathecal Injection in the Rat

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The A1-adenosine receptor agonist, R-phenylisopropyl-adenosine (R-PIA), demonstrated antinociceptive properties in animal studies after intrathecal administration. In the evaluation of a drug for possible spinal injection in humans, the effects of intrathecal R-PIA on spinal cord blood flow (SCBF) were investigated using the laser-Doppler flowmetry technique in anesthetized rats. In low doses (0.1–1 nmol), no change in SCBF was recorded, whereas larger doses (10–100 nmol) caused a significant increase in SCBF. No change in systemic arterial blood pressure could be seen, except for a decrease after administration of the largest dose of R-PIA (100 nmol). It is concluded that R-PIA in doses of 10 nmol and larger induces an increase in SCBF after intrathecal injection in anesthetized rats and that an increase in blood flow is seen before any effect on the systemic circulation is detected. It can also be deduced that the antinociceptive effects of R-PIA after intrathecal injection are not a consequence of spinal ischemia and that disturbances in local blood flow cannot be expected to constitute a neurotoxic factor.

(Anesth Analg 1992;75:972–6)

Intrathecal injection of the adenosine analogue R-phenylisopropyl-adenosine (R-PIA) induces antinociceptive effects in several nociceptive tests in rats (1–8) and mice (9–12). The effects are mediated through activation of extracellular adenosine receptors that have been classified according to Van Calker et al. (13) as A1- and A2-receptors. Both types have been identified in the rat spinal cord using autoradiographic methods (14). The antinociceptive effects of intrathecally administered adenosine agonists are probably mediated through activation of spinal A1-adenosine receptors (12). R-Phenylisopropyl-adenosine, which has a high affinity for the A1-receptor (15), also induces motor impairment in rats after intrathecal injection of large doses (>10 nmol), but it is possible to separate the antinociceptive effect from the motor impairment using smaller doses (8). This has indicated that R-PIA is a potential drug for future pain treatment in humans (8,12).

Before using new drugs for spinal administration in humans, animal studies on neurotoxicity must be performed. These should include histologic examination of the spinal cord after long-term exposure to the test drug, as well as evaluation of the effect of the drug on spinal cord blood flow (SCBF) (16–19). The reason for investigating the effects on SCBF is that severe vasoconstriction may produce spinal cord ischemia and thus give rise to structural lesions. Another reason for studying SCBF is that disturbances in local blood flow in the spinal cord could influence the results of behavioral and physiologic experiments (20).

With this background, the present study was conducted to evaluate the effects of increasing doses of R-PIA on SCBF measured with laser-Doppler flowmetry technique after intrathecal administration in rats.

Methods

The study was approved by the local ethical committee for animal experiments. Nine male Sprague-Dawley rats (obtained from ALAB, Sollentuna, Sweden) weighing 350–430 g were housed in animal rooms thermostatically maintained at 20°C, with artificial lighting (12 h/day) and free access to food and water, for 5–7 days before the experiment. The animals were anesthetized with O_2/N_2O (1 L/min of each) and enflurane (4% during induction of anesthesia, then reduced to 2% during the surgical procedure and to 1.5% during measurements). The animals were breathing spontaneously through a mask. The temperature was kept constant at 37°C throughout the experiment by use of a heating blanket placed under

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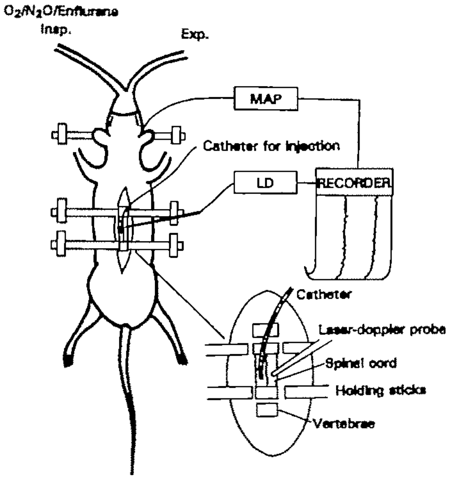

Figure 1. Experimental setup. The rat is held by a stereotactic frame. Mean arterial blood pressure (MAP) and the laser-Doppler signal (LD) are monitored on a two-channel strip-chart recorder.

the rat and controlled by a temperature probe placed in the rectum of the animal. A catheter was inserted into the right common carotid artery for continuous measurement of arterial blood pressure and for analysis of arterial blood gases. The spinal cord was exposed by bilateral laminectomy over the lumbar T13 to L2 region without rupturing the dura. The animals were then placed in a stereotactic frame, allowing fixation of the vertebrae to make certain that there were minimal respiratory movements of the spinal cord. A dissection microscope was used to guide the intrathecal insertion of a polyethylene catheter (PE 10, previously stretched in warm water to reduce the outer diameter) approximately 5 mm through a slit in the dura to the left side of the central vein.

The SCBF was measured using laser-Doppler flowmetry technique (21,22). This method records the relative change in blood flow over time in a tissue volume constituting a hemisphere with a radius of approximately 1 mm (21). We used a Perimed model Pf2b laser-Doppler instrument (Stockholm, Sweden). The laser-Doppler probe (Pf 303) was positioned to the right side of the central vein, just above the surface of the spinal cord, to give a high-quality signal. The readings were recorded on a two-channel strip-chart recorder. Mean arterial blood pressure was continuously monitored, and the readings were recorded on a two-channel strip-chart recorder. This was done to ascertain that changes in SCBF were not secondary to changes in central hemodynamics. The experimental setup is shown in Figure 1.

Arterial blood samples (200 μL) were drawn before intrathecal injections started and at the end of the experiment before injection of epinephrine. Blood gases were analyzed because changes in $Paco_2$ and Pao_2 have profound effects on cerebral and spinal vascular resistance and blood flow (23–25).

The R-PIA (Boeringer, Mannheim, Germany) was dissolved using a few drops of HCl, buffered to a pH of 7 with NaOH and then diluted in 0.9% saline to concentrations of 0.01, 0.1, 1.0, and 10 μM. When the experimental setup had stabilized, usually after 30–45 min, an arterial blood sample was drawn for blood gas analysis, and 25 μL of 0.9% saline was injected intrathecally as a control (each animal served as its own control). Twenty minutes after the injection of saline, R-PIA was injected in increasing doses of 0.1, 1.0, 10, and 100 nmol, with 20–25-min intervals between the doses. This time interval was chosen to allow stabilization of the readings. After the injection of 100 nmol of R-PIA, a blood sample for blood gas analysis was drawn. Each rat received a dose of 1 μg of epinephrine at the end of the experiment as a positive control for vasoconstriction (26,27). All drugs were injected in a volume of 10 μL, followed by a flush of 15 μL of 0.9% saline to clear the catheter. The temperature of the injected solutions was constantly 20°C. The animals were then killed by inhalation of 100% N_2O to achieve a zero baseline for the recordings of SCBF and arterial blood pressure.

The results of the laser-Doppler and blood pressure measurements are presented as percent of predrug values ± SEM. These data were analyzed using one-factor analysis of variance for repeated measures (Scheffé F-test). The arterial blood gas data are presented as mean ± SEM. Wilcoxon's signed rank test was used to calculate statistical differences. A statistically significant difference was assumed at $P < 0.05$.

Results

Spinal injection of saline and low doses of R-PIA (0.1–1 nmol) had no effect on SCBF. After administration of 10 and 100 nmol of R-PIA, a statistically significant increase in SCBF was seen. The increase occurred during a 15–20-min period, after which the blood flow stabilized and stayed at an increased level (Figure 2). When epinephrine was injected, a significant reduction in SCBF was recorded that stabilized at a lower level after 5 min (Figure 2). The systemic arterial blood pressure was unchanged until the highest dose (100 nmol) of R-PIA was administered. This caused a significant reduction (Figure 3) that also stabilized at a lower level within 20 min. Intrathecal injection of 1 μg of epinephrine did not alter the arterial blood pressure, which had already been decreased by 100 nmol of R-PIA. The arterial oxygenation was stable throughout the experiment, and $Paco_2$ and pHa were unchanged (Table 1).

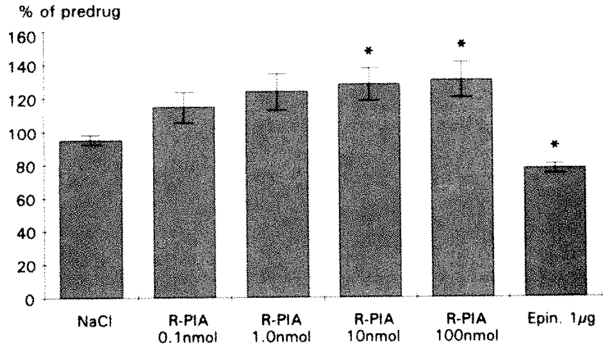

Figure 2. Spinal cord blood flow at steady state measured with laser-Doppler flowmetry technique after intrathecal administration of increasing doses of R-PIA. Values (% of predrug) are expressed as mean ± SEM; $n = 9$. *$P < 0.05$. Epin., epinephrine.

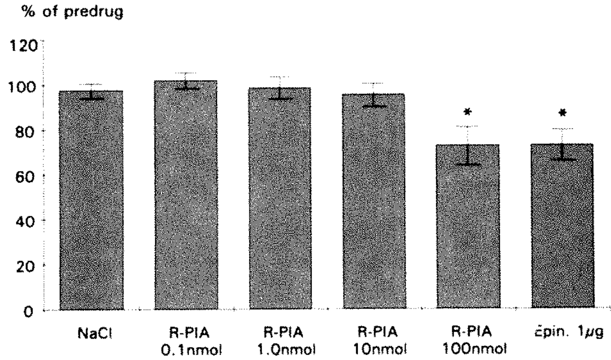

Figure 3. Mean arterial blood pressure after intrathecal administration of increasing doses of R-PIA. Values (% of predrug) are expressed as mean ± SEM; $n = 9$. *$P < 0.05$. Epin., epinephrine.

Discussion

The present study shows that R-PIA induces a significant increase in SCBF after intrathecal injection of 10 and 100 nmol in the rat. The increase occurred within 20 min and stayed at an increased level compared with the predrug recording. With smaller doses, no significant change in SCBF could be seen.

These results clearly indicate that the antinociceptive effects of R-PIA, which reach their maximum in the rat within 15–30 min after intrathecal administration (8), are not accompanied by a decrease in SCBF. The laser-Doppler probe was situated just above the dorsal horn of the spinal cord, and for this reason we conclude that the nociceptive effects of R-PIA are not due to neuronal ischemia. The increase in SCBF after 10 nmol of R-PIA was probably not a consequence of altered systemic circulation, because no effect could be seen on the systemic arterial blood pressure during the 20-min observation period. Conversely, injection of 100 nmol of R-PIA was followed by a significant decrease in systemic arterial blood pressure. This large dose induces severe motor impairment and sedation in the rat after intrathecal administration (8). It is 100 times larger than the smallest dose (1 nmol) of R-PIA that induces antinociception in the rat after intrathecal injection (7). The effect is probably systemic, because adenosine and its derivatives in large doses have profound effects on the systemic circulation (28–31), but it may also be mediated through spinal mechanisms as the decrease in arterial blood pressure could be seen almost immediately after the intrathecal injection (data not shown).

Freedman et al. (32) reported that the substance-P antagonist [D-Arg,D-Trp,Leu]-substance P (Spantide) decreased SCBF, as assessed using laser-Doppler and iodoantipurine tests. It was proposed that this may be the reason for neurotoxic effects seen after intrathecal administration of Spantide in rats. As no decrease in SCBF could be seen in the present study with R-PIA, disturbances in SCBF cannot be expected to constitute a neurotoxic factor.

No change in arterial blood gases could be seen after intrathecal injection of R-PIA. The slight increase in Pa_{CO_2} throughout the experiment is probably due to the respiratory depression caused by inhaled anesthetic.

There are advantages in using the laser-Doppler method when studying SCBF. It provides a continuous recording over time in the same animal, thus allowing increasing doses to be administered. However, because it only measures the relative change in blood flow in a tissue hemisphere of approximately 1 mm in radius (21), no conclusions can be drawn about the distribution of blood flow in the spinal cord. The method also includes measurements of blood flow in the dura, but the significance of this is probably small, because blood flow in the dura is relatively low compared with the spinal cord. Using the radioactive microsphere technique in dogs, Kozody et al. (33) have shown that the lumbosacral SCBF was approximately 25 mL·100 g^{-1}·min^{-1}, whereas the dural blood flow in the same region averaged approximately 4.3 mL·100 g^{-1}·min^{-1}.

The laser-Doppler probe measures a restricted volume within the spinal cord. In the present study, we attempted to place the probe at the site of the dorsal horn. It is not possible to place the probe in exactly the same spot in all animals, and the distance between the tip of the intrathecal catheter and the laser-Doppler probe cannot be standardized. The differences in the location of the laser-Doppler probe influence the ratio of gray/white substance in the tissue volume under the probe. Taking these factors into account, we used the individual animal as its own control and compared the injection of saline with the different doses of R-PIA. The intention of the study was not to produce a true dose response, but to screen for potential reduction in SCBF that might

Table 1. Arterial Blood Gases Before Intrathecal Injection of R-Phenylisopropyl-Adenosine (Predrug) and at the End of the Experiment, After Administration of 100 nmol R-Phenylisopropyl-Adenosine (Postdrug)

	pH (U)	Pa_{CO_2} (kPa)	Pa_{O_2} (kPa)	Base excess (mM)	O_2 saturation (%)	Standard bicarbonate (mM)
Predrug	7.39 ± 0.03	5.9 ± 0.5	22.6 ± 4.1	0.9 ± 0.6	97.4 ± 0.8	25.1 ± 0.6
Postdrug	7.41 ± 0.02	5.2 ± 0.3	27.7 ± 3.3	0.2 ± 0.4	98.9 ± 0.3	24.6 ± 0.4

Values are expressed as mean ± SEM.

have neurotoxic effects. The SCBF did not return to baseline between injections, but the incremental doses were 10-fold higher, making the previous dose almost negligible. If we had permitted the SCBF to return to baseline, the experiment would have been several hours longer. The antinociceptive effect of R-PIA after intrathecal injection in the rat reaches its maximum within 15–30 min (8). If the antinociceptive effect of R-PIA was a consequence of spinal ischemia, then an observation period of 20 min after each dose should be sufficient.

Because the laser-Doppler method does not measure the distribution of blood flow within the spinal cord, other methods should also be used before drawing conclusions about the effects of a drug on SCBF. One such method is the iodoantipurine method, in which the absolute change in blood flow and the distribution within the spinal cord can be studied (24,34). Using this method, we have demonstrated that intrathecal injection of 10 nmol of R-PIA induced a significant increase in the gray matter in the lumbar spinal cord (J.D. Kristensen et al., unpublished observations). These results are compatible with the results in the present laser-Doppler experiment.

Adenosine induces vasodilation in most tissues, except the placenta and the kidney (35). Several authors have reported the effects of adenosine and adenosine analogues on cerebral blood vessels and cerebral blood flow. The results are conflicting. There have been reports that adenosine analogues either increase (36) or decrease (37,38) cerebral blood flow. In a study by Norlén (30), the infusion of adenosine in pigs for deliberate hypotension increased SCBF, whereas cerebral blood flow was unchanged.

It was previously shown by Edvinsson and Fredholm (39) that adenosine and adenosine analogues dilate cerebral arteries. The rank order of potency indicated that the dilation was mediated through activation of adenosine A2-receptors. This might explain why, in the present study, the A1-agonist R-PIA increased SCBF to 30%, at most, above the predrug value.

R-phenylisopropyl-adenosine administered intravenously in rats induces a decrease in blood flow in some areas in the brain, as was demonstrated in a recent study by Nehlig et al. (38). In that study, R-PIA also decreased arterial blood pressure by 48%, which makes it difficult to conclude whether the effects on the cerebral circulation are direct or indirect. The dose of R-PIA administered was 0.1 mg/kg, which corresponds to the highest dose in our study (100 nmol). This should be compared with the smallest dose needed for antinociceptive effects after intrathecal injection in the rat (1 nmol).

It must be emphasized that the present study was conducted to screen for potential decrease in SCBF after intrathecal injection of R-PIA. No conclusion can be drawn about other possible toxic effects of the drug. Even if the arterial blood gases drawn at the end of the experiment were normal, this does not constitute evidence that R-PIA, even in small doses, is without effects on respiration or central hemodynamics. The observation period after the largest dose was not sufficiently long in the present study, nor was it the focus of the study to evaluate this.

In the present study, epinephrine induced a significant decrease in SCBF compared with saline. It is still not clear whether epinephrine induces a decrease in SCBF when injected alone intrathecally. Using the microsphere technique in dogs, Kozody et al. (40) demonstrated that the intrathecal injection of epinephrine did not alter SCBF. In another study by Kozody et al. (41), using the same technique in dogs, tetracaine was shown to increase SCBF. When tetracaine was injected together with epinephrine, no change in SCBF compared with controls could be seen. For this reason, we cannot draw any conclusions as to the effects of epinephrine on SCBF other than that it did reduce SCBF, which had previously been increased by R-PIA. Dohi et al. (27) reported that ephedrine decreases SCBF, and in a study by Edvinsson and Owman (26), it was shown that epinephrine was a potent mediator of vasoconstriction in cerebral arteries.

In summary, the adenosine receptor agonist R-PIA in doses of 10 nmol and larger induces a significant increase in SCBF within 20 min after intrathecal injection in the rat. In doses up to 10 nmol, no effect could be seen on systemic arterial blood pressure, but a large dose (100 nmol) significantly decreased arterial blood pressure. We also conclude that the antinociceptive effects of R-PIA after intrathecal injection are not a consequence of spinal ischemia and that disturbances in SCBF cannot be expected to constitute a neurotoxic factor.

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Changes in Functional Residual Capacity and Regional Diaphragm Lengths After Upper Abdominal Surgery in Anesthetized Dogs

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The respiratory performance of the diaphragm may be altered by changes in mechanical or neural factors, or both, induced by upper abdominal surgery. We conducted this study to examine the effects of upper abdominal surgery on postoperative respiratory function. We studied resting lengths of four diaphragm regions, three in the costal and one in the crural diaphragm, with biplane videoroentgenography in six dogs immediately after upper abdominal surgery and up to 30 days postoperatively. Functional residual capacity was 16.7% smaller immediately after surgery compared with values obtained in the same animals after 30 days. Simultaneously measured resting lengths of each of the diaphragm regions immediately after surgery were longer, on average by 8.3%, than 30 days postoperatively. During the postoperative course, resting diaphragm lengths gradually and uniformly decreased as functional residual capacity increased. Phrenic nerve stimulation in four other dogs immediately after identical surgery resulted in large diaphragm shortening (from 42% to 55%), indicating that neither the diaphragm nor phrenic nerves were injured by the surgical manipulation. We hypothesize that respiratory dysfunction after upper abdominal surgery may be, at least in part, attributed to a decreased central drive for breathing caused by activation of the afferent limb of an inhibitory reflex owing to stretching of the diaphragm.

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Postoperative respiratory dysfunction occurs after upper abdominal surgery (UAS) (1–6) and is caused by inhibition of central respiratory drive, not mechanical dysfunction of the diaphragm (2,7,8). Afferent traffic from the diaphragm, if it is stretched, inhibits breathing (9). Because functional residual capacity (FRC) is decreased in patients after UAS (3), and because we have found that diaphragm length varies inversely with lung volume in dogs (10), we postulated that part of the respiratory dysfunction may be attributed to the inhibition of breathing secondary to an increase in diaphragm stretch. However, results from the two previous studies that have measured diaphragm resting length using sonomicrometry during recovery from UAS seem to contradict this. In awake, standing sheep, there was no change in resting length of the crural diaphragm, and there was a shortening of the costal region after UAS compared with recovery (8). In awake dogs, there were no significant changes of the crural or costal diaphragm compared with 22 days after surgery (11). Because FRC was not measured in these studies, it is difficult to evaluate the applicability of these results to humans. Presently, there is no study that simultaneously correlates FRC and resting diaphragm length after UAS.

In this study, we quantified resting lengths of four regions of the diaphragm by using computerized biplane-videoroentgenography (12) immediately after UAS and during the 30-day recovery period. We were able to correlate postoperative regional length changes in FRC. We conclude that postlaparotomy respiratory dysfunction is, at least in part, due to decreased central respiratory drive caused by reflex inhibition originating from afferents in the stretched diaphragm.

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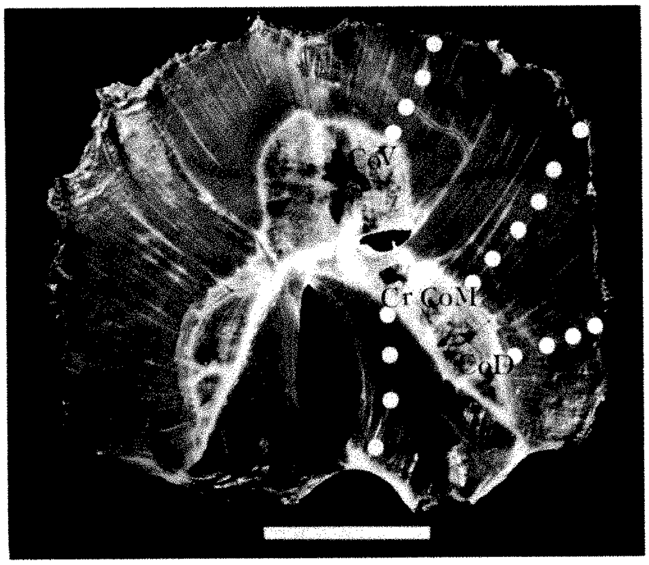

Figure 1. Excised canine diaphragm (abdominal side) showing schematically the typical location of markers sutured along muscle bundles in the ventral (CoV), middle (CoM), and dorsal (CoD) regions of the costal diaphragm and in the crural (Cr) diaphragm. The actual markers were lead beads, 2 mm in diameter, relatively smaller than the *white dots* shown here. The regional diaphragm length was calculated as a cumulative sum of all intermarker distances. *White bar* = 8 cm.

Methods

Study approval was obtained from the Institutional Animal Investigation Committee. Ten beagle dogs (10–13 kg) were anesthetized with pentobarbital (30 mg/kg, supplemented as needed), tracheally intubated with a cuffed endotracheal tube (inner diameter 9 mm) without neuromuscular blocking agents, and mechanically ventilated. After induction of anesthesia, a midline laparotomy was performed under sterile conditions. Silicone-coated lead spheres (2-mm diameter) with central holes were stitched with 5-0 Prolene to the peritoneal serosa of the left hemidiaphragm. The rows of spheres, which served as radiographic markers, were placed along muscle bundles from the insertion of the diaphragm on the rib cage to their origin on the central tendon. The spheres were spaced at 1.5–2.0-cm intervals so that the sum of the intermarker distances would closely approximate the arc length along the diaphragm region (12). Figure 1 shows the four regions in which the markers were located: the ventral, middle, and dorsal portion of the costal diaphragm and the crural diaphragm region.

All measurements of resting diaphragm lengths and FRC were made with the dogs anesthetized and spontaneously breathing. Anesthesia was induced with pentobarbital (30 mg/kg); sufficient supplemental doses (10%–20% induction dose) were administered to abolish spontaneous movements. Regional diaphragm resting length was measured in six dogs on the same day of marker placement, 4–8 h after surgery (OD) and on postoperative day (POD) 30. In addition, measurements were made on POD 3 and 15 in four of the dogs. The dogs were placed supine in a radiolucent volume-displacement body plethysmograph in the center of an orthogonal biplane videoroentgenographic system. The lower rib cage and upper abdomen, with the diaphragm markers, were scanned during consecutive breaths. If fluoroscopy revealed signs of residual postlaparotomy pneumoperitoneum, the air was evacuated with needle aspiration before studies of the diaphragm were attempted. The animals breathed through a Fleisch pneumotachograph that measured flow, and thoracic gas volume was measured at FRC by Boyle's law during inspiratory efforts against an occluded airway. The fluoroscopic images were encoded on a stop-action videotape. We also measured regional diaphragm shortening during 15 spontaneous breaths and during mechanical ventilation (Harvard pump). For the latter measurements, the same tidal volume as spontaneous breathing was used. Initially, a respiratory frequency more rapid than spontaneous breathing was used to ensure inhibition of breathing efforts. Then, the frequency was reduced to that observed during spontaneous ventilation, and 15 mechanical breaths were recorded. During these breaths, there was no evidence of spontaneous respiratory efforts in any of the dogs. After all data were recorded, each of the six dogs was killed with an overdose of barbiturate. Macroscopic and microscopic (histologic slides) examination of the diaphragm did not show any signs of significant inflammation or other abnormalities.

In four additional dogs, the phrenic nerves were electrically stimulated to determine the extent of maximal diaphragm shortening shortly after surgical manipulation identical to that used in the other six dogs. The cervical roots comprising the phrenic nerve (C5–7) were identified and isolated on both sides of the neck. Insulated hook electrodes were placed under the nerve roots and covered with mineral oil. The phrenic nerves were stimulated with 50 Hz using a Grass S88 nerve stimulator. Diaphragmatic shortening was measured during three consecutive phrenic nerve stimulations.

The projection of each marker in the two orthogonal fluoroscopic images was identified by an operator-interactive computer program. A cursor was moved in regular numerical order along the rows of markers on both views of the same video frame. Once the geometric coordinates of all the parenchymal markers in the first frame had been entered, at FRC, the same sequence was repeated at the end of inspiration. The distance between individual markers was computed from the three-dimensional spatial coordinates of each marker using solid geometry. The regional diaphragm length was calculated as the sum of individual intermarker lengths. Regional diaphragm shortening was expressed as relative changes in length at end-inspiration from the length at FRC (resting length). "Average" diaphragm shortening was calculated by finding the mean shortening of the four regions in each dog and then finding the average of this mean in the six dogs.

The biplane videoroentgenography technique does not allow preoperative control values to be established, because the diaphragm markers require surgical placement. However, in a previous long-term study in dogs (12), diaphragm regional length and shortening 2 mo postoperatively were similar to that 30 days after surgery, indicating that 30 days after UAS, diaphragm function has recovered to its preoperative baseline level. Because there were no significant differences among regional diaphragm shortening or lengths on POD 15 and 30 in this study, we assume that recovery was achieved by POD 15.

All data are presented as mean and SEM. One-way analysis of variance for repeated measures was used for all paired comparisons for each variable. The Fisher Least Square Difference test was used to compare the statistical significance between repeated measurements. A level of $P < 0.05$ was considered statistically significant.

Results

Mean respiratory frequency immediately postoperatively was 7.5 ± 1.5 breaths/min, less frequent ($P < 0.05$) than on POD 30 (16.9 ± 5.8 breaths/min). Tidal volumes gradually increased from 135 ± 31 mL on OD to 160 ± 33, 235 ± 43, and 240 ± 46 mL on POD 3, 15, and 30, respectively. Significant differences ($P < 0.05$) in tidal volume were found between OD and all other days and among POD 3, 15, and 30.

The regional diaphragm lengths and FRC after UAS are shown in Figure 2. The FRC was lower on OD compared with POD 3, 15, and 30 ($P < 0.05$). Although there was a trend for FRC to further increase after POD 3, this increase was not statistically significant. Immediately postoperatively, all diaphragm regions were longer than on POD 30 ($P < 0.05$). The average length of the four diaphragm regions on OD was 8.3% ± 0.8% longer than on POD 30 (range 7%–11%). Diaphragm resting lengths in the postoperative period were inversely correlated with FRC. The correlation coefficients between FRC and the diaphragm lengths were as follows: $r = -0.98$ for the ventral and middle, -0.92 for the dorsal, and -0.97 for the crural portions.

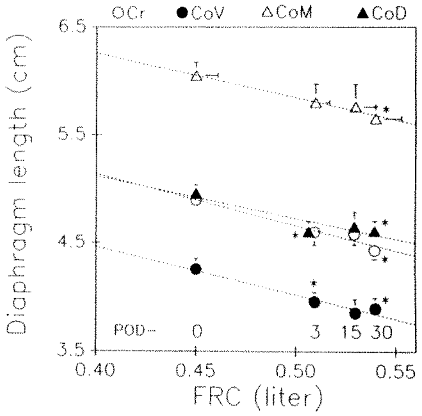

Figure 2. Resting diaphragm lengths at functional residual capacity (FRC) and corresponding FRC after upper abdominal surgery; linear regressions are indicated by *dashed lines*. The FRC was significantly lower on the day of surgery compared with postoperative days (POD) 3, 15, and 30. POD 0 and 30, $n = 6$; POD 3 and 15, $n = 4$. *Difference from POD 0 ($P < 0.05$). SEM indicated by *vertical and horizontal bars*. Other abbreviations as in Figure 1.

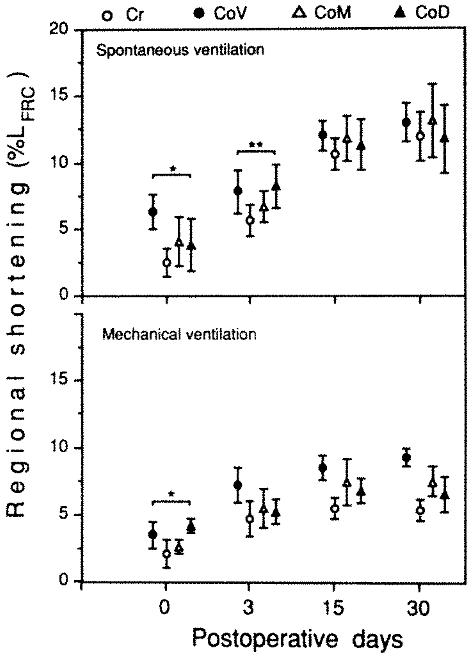

Figure 3. Regional diaphragmatic shortening, expressed as percent resting length at functional residual capacity (%L_{FRC}), during spontaneous and mechanical ventilation after upper abdominal surgery. SEM indicated by *vertical bars*. Postoperative days 0 and 30, $n = 6$; postoperative days 3 and 15, $n = 4$. *Difference in average tidal breath shortening from postoperative days 3, 15, and 30 ($P < 0.05$). **Difference in average tidal breath shortening from postoperative days 15 and 30 ($P < 0.05$). Other abbreviations as in Figure 1.

Figure 3 shows regional diaphragmatic shortening during spontaneous and mechanical ventilation. "Average" diaphragmatic shortening during spontaneous breathing was decreased ($P < 0.05$) in the immediate postoperative period compared with

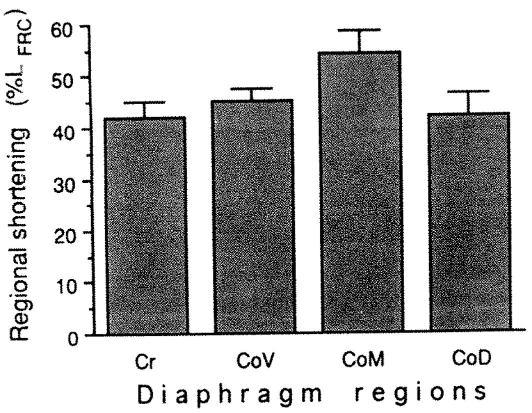

Figure 4. Regional diaphragmatic shortening during bilateral phrenic nerve stimulation in four dogs, expressed as percent resting length at functional residual capacity ($\%L_{FRC}$). SEM indicated by *vertical bars*. Other abbreviations as in Figure 1.

PODs 15 and 30. Over the first 15 PODs, the diaphragmatic shortening gradually increased, and by POD 15 the diaphragmatic shortening was comparable to POD 30 ($P > 0.05$). Diaphragmatic shortening during mechanical ventilation was decreased on OD compared with PODs 3, 15, and 30 ($P < 0.05$). The ratio of the average shortening in the four diaphragm regions to tidal volume increased during spontaneous ventilation from 31% ± 3% per liter on OD to 49% ± 2% per liter on POD 30. During mechanical ventilation, the ratio increased from 23% ± 3% per liter on OD to 32% ± 3% per liter on POD 30. Figure 4 shows regional diaphragmatic shortening after phrenic nerve stimulation in four dogs. All regions shortened at least 42% after the stimulation.

Discussion

Biplane videoroentgenography necessitates the use of anesthetized animals because any gross body movement may result in erroneous measurement. However, barbiturate anesthesia does not affect FRC in supine dogs (13), and the changes in FRC displayed by the anesthetized dogs in our study were similar to those seen in most patients after UAS (3). In contrast, in awake animals FRC does not seem to change after UAS, as inferred from only small, inconsistent changes in resting diaphragm lengths (8,11). Thus, the anesthetized dog seems a fitting model for the clinical situation. It is also probable that the prolonged period of anesthesia and surgical trauma on the day of marker implantation in the dogs is roughly comparable to those encountered in many abdominal surgeries, because one could expect wide variabilities in patient response to anesthesia and in difficulty of surgery. It is unlikely that the presence of the marker beads on the diaphragm exerted effects on afferent stimulation independent of the surgery, because extreme care was taken during surgical implantation, and the markers were sutured to the serosa of the diaphragm undersurface, thus sparing muscle bundles. In summary, the protocol used in the present study offers some advantages over other animal studies, and the results should be reasonably applicable to the clinical situation.

According to Craig (3), during POD 1 after UAS, the FRC decreases up to 30% and gradually returns toward normal over 7–10 days. This change in FRC is probably not immediate, because Dureuil et al. (2) did not find significantly reduced FRC 4 h after cholecystectomy. We found a distinct decrease in FRC 4–8 h after UAS that gradually recovered by POD 15. In our study, the regional diaphragm length at FRC was inversely related to FRC and decreased relatively uniformly throughout the recovery period. In contrast, Torres et al. (8) found that after laparotomy in awake sheep, costal resting length was decreased 17% ($P < 0.01$) on POD 1 compared with POD 7, whereas the crural resting length remained unchanged throughout the recovery. Easton et al. (11) found different trends in awake, resting dogs: costal resting length at FRC increased 1.56 mm, whereas crural length decreased 1.93 mm, both approximately 11% compared with recovery. However, these length changes were not significant. The videoroentgenography technique allows us to measure length change of a relatively large diaphragm segment (4–6 cm) compared with the small segment (1–1.5 cm) measured with sonomicrometry. In our previous study (12), as well as in this one, we found that there were significant differences in intraregional fractional shortenings and that no single location was representative of the shortening of the entire diaphragm. This is in contrast to the report of uniform shortening across the diaphragm segment (14). Videoroentgenography, which measures the length of the entire diaphragm region by summing all intraregional separations between markers, should give a more accurate estimate of global regional diaphragm behavior than sonomicrometry. However, because the studies using sonomicrometry (8,11) did not measure FRC, it is not possible to decide whether discrepancies among resting lengths in their and our experiments were due solely to limitations of sonomicrometry technique or additionally due to species differences and protocol.

The decreased FRC and increased diaphragm length after upper abdominal surgery may be at least partly due to activation of expiratory muscles. Duggan and Drummon (15) reported increased expiratory activation of the abdominal external oblique muscle in humans after cholecystectomy. Farkas and De Troyer (16) found that expiratory activation of the triangularis sterni muscle was maintained or increased after laparotomy in dogs. Activation of expiratory muscles may cause cephalad displacement of the diaphragm. The cephalad diaphragm displacement will result in decreased FRC and elongated crural and costal diaphragm parts (17). Whether other factors also contribute to the decrease in FRC after UAS is not clear.

Although some workers have suggested that mechanical diaphragm dysfunction due to local irritation, inflammation, or trauma secondary to UAS may be responsible for alteration in contractile properties of the diaphragm (1,5), recent evidence suggests that decreased respiratory drive due to afferent inhibitory traffic is primarily involved (7,8,18). Immediately postoperatively, the dogs in our study displayed much lower minute ventilation (owing to reduction of both tidal volume and respiratory frequency) than on POD 30, which suggests a centrally mediated mechanism of respiratory dysfunction. In addition, evidence from our results is consistent with the conclusion that respiratory dysfunction is not primarily due to mechanical impairment of the diaphragm. First, regional shortening to phrenic nerve stimulation on OD was at least 42% in each region of the diaphragm. The shortening that we found is in a range similar to that described in dogs or sheep during phrenic stimulation after recovery from surgery (8,11). This indicates that our method, which uses implantation of up to 18 markers on the diaphragm undersurface, did not physically impair diaphragmatic ability to contract. Second, during both spontaneous and mechanical ventilation, the ratio of average regional shortening to tidal volume was less on OD than on POD 30. One might expect that the ratio would be increased if a given amount of diaphragmatic shortening was less effective in increasing lung volume. It is possible, but unlikely, that an extremely abnormal pattern of respiratory muscle activation could cause such a change during spontaneous breathing; however, this might not be the case during mechanical ventilation. Rather, passive changes in chest wall mechanics, such as the observed decrease in FRC, and the likely decrease in abdominal compliance (15) probably affected the ratio. In any case, the results indicate no gross mechanical dysfunction of the diaphragm.

There is evidence that increased diaphragmatic stretch, as observed in the present study, could lead to decreased respiratory drive. Cheeseman and Revelette (9) demonstrated that an increase in diaphragmatic operating length decreases phrenic nerve efferent drive, an effect abolished after bilateral cervical dorsal root transection. The increase in diaphragm length tested was approximately 17%, measured with sonomicrometry. It is difficult to directly compare localized sonomicrometric measurements with our more global measurements. However, the range of immediate postoperative stretch in our study was only slightly less, between 7% and 11%, and it is likely that increased diaphragmatic stretch activated inhibitory diaphragmatic afferents. Such a conclusion is consistent with the report by Jammes et al. (19) that muscle spindle and Golgi tendon organ receptors in the diaphragm reflexly inhibited phrenic motor output through phrenic afferents. It should be mentioned that in addition to afferent inhibition from the diaphragm, afferents from other sources could be involved. For example, it has been demonstrated that intercostal and abdominal muscle proprioceptors (20), afferents from the gallbladder (21), and cutaneous afferents in an area of the chest wall where the diaphragm inserts on the ribs (22) could decrease respiratory drive. However, epidural block with local anesthetic up to the T4 level only partially reversed respiratory dysfunction after UAS (17), whereas epidural analgesia had no effect (5,23). Because suppression of vagal inputs and spinal afferents below C8 does not prevent the inhibition of phrenic motoneuron activity due to stimulation of phrenic afferents (19), it is probable that a phrenic-phrenic reflex is involved with inhibition of breathing after UAS.

In conclusion, decreased central respiratory drive after UAS could be due in part to reflex inhibition originating in receptors in the stretched diaphragm, such as Golgi tendon organs.

The authors are indebted to Dr. Claude Deschamps, who performed the surgery in the dogs.

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Ethanol Monitoring of Transurethral Prostatic Resection During Inhaled Anesthesia

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The purpose of this study was to examine the precision of a method of breath-alcohol analysis used to monitor absorption of irrigating fluid during transurethral resection of the prostate performed under inhaled anesthesia. A breath-alcohol analyzer (Alcolmeter SD-2) was placed between the endotracheal tube and the Bains' circuit. The concentration of ethanol in the breath, serum sodium concentration, and volumetric fluid balance were measured at 10-min intervals during 38 operations when the irrigating fluid contained 1.5% glycine and 1% ethanol. Ethanol monitoring detected absorption rates that exceeded 14 ± 8 mL/min (mean ± SD). In 17 patients in whom hyponatremia developed immediately in connection with absorption, the volume of irrigating fluid absorbed (up to 1950 mL) could be predicted from a single expired-breath test with a standard error of 325 mL. When the alcohol measurements were corrected for absorption time, the standard error was 215 mL. Seven other patients received 2.2% wt/vol glycine as irrigating fluid, and ethanol (0.35 g/kg) was administered by intravenous infusion. The direct and indirect measurements of the blood-alcohol concentration agreed well. These results confirm that ethanol monitoring is a viable technique during inhaled anesthesia for transurethral resection of the prostate.

(Anesth Analg 1992;75:983–8)

Transurethral resection of the prostate (TURP) is usually performed under regional anesthesia. In 5%–10% of patients, symptoms associated with absorption of irrigating fluid occur that may develop into the potentially life-threatening "TUR syndrome" (1–3). The use of irrigating fluid containing a trace amount of ethanol and the subsequent measurement of ethanol in the patient's exhaled breath (EB) is a reliable, noninvasive method to detect absorption of irrigating fluid (1–5).

The aim of the present study was to evaluate the precision of ethanol monitoring in patients undergoing TURP performed under inhaled anesthesia. We measured the volumetric fluid balance and the serum sodium concentrations during 38 TURPs. The results were compared with the ethanol in EB (EB-ethanol) concentration, which was measured by an Alcolmeter device that was connected between the endotracheal tube and the breathing circuit. Furthermore, the accuracy of the EB measurements in patients under general anesthesia was examined by comparing the concentration-time profiles of ethanol in venous blood and breath in seven patients who received an intravenous infusion of ethanol.

Methods

We studied 45 patients (mean age 69 yr, range 43–87; mean body weight 79 kg, range 60–103) who underwent TURP for benign prostatic hypertrophy. All of the patients gave informed consent to participate, and the study protocol was approved by the Ethics Committee of the Huddinge University Hospital.

Oxycodone (2.5–12.5 mg) and scopolamine (0.1–0.5 mg) ($n = 40$) or meperidine (50 mg) ($n = 5$) were administered intramuscularly 30 min before arrival in the operating room. Anesthesia was induced with thiopental (2.5–5 mg/kg IV) and fentanyl (0.1 mg IV). Tracheal intubation was facilitated with succinylcholine (1 mg/kg), sometimes preceded by pancuronium (1 mg) or atracurium (5 mg). Anesthesia was maintained with a 6–8-L/min fresh gas mixture of nitrous oxide/oxygen (70%:30%) and 0.5%–1.5% of inspired enflurane ($n = 42$) or isoflurane (0.5%–1.0%) ($n = 3$) provided through a Bains' circuit. Ventilation was controlled, and electrocardiography was monitored continuously. Ringer's acetate solution (sodium 130 mmol/L, potassium 4 mmol/L) was administered

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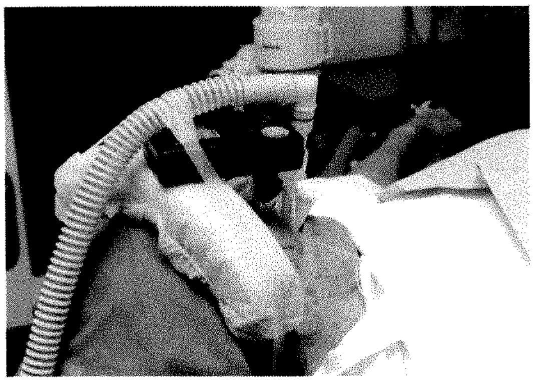

Figure 1. Tracheally intubated patient with the Alcolmeter device connected between the endotracheal tube and the Bains' circuit.

by intravenous infusion at a rate of 50–150 mL over 10 min during TURP, depending on the amount of blood lost. In six patients, where blood loss exceeded 500 mL, 500 mL of dextran 70 in normal saline was also administered.

The EB-ethanol concentration was measured every 5 min during the operation by an a fuel cell-type alcohol sensor (Alcolmeter S-D2, Lion Laboratories Ltd., South Glamorgan, Wales). The presumed venous blood alcohol concentration was estimated based on a calibration factor of 2300:1 for the blood/breath ratio of ethanol. The Alcolmeter device was calibrated using alcohol-in-air gas standards at 0.80 mg/mL equivalent blood alcohol, and readings could be taken to within 0.05 mg/mL. A 2-mm hole was drilled in a Capnomac straight T-adapter (Datex, Helsinki, Finland), which was placed between the endotracheal tube and the ventilation system (Bains' circuit). The inlet to the Alcolmeter device was directly connected to the hole in the T-piece and positioned on the patient's forehead, as shown in Figure 1. Before an EB sample was taken, a triple tidal volume was inflated, and the EB-ethanol concentration was measured at the end of the passive expiration. Preliminary experiments showed that the Alcolmeter readings were not affected by nitrous oxide, isoflurane, or efrane.

In 38 of the patients, a solution of 1.5% glycine and 1% ethanol was used to irrigate the bladder. Blood loss and volumetric fluid balance were measured every 10 min during TURP, always at the same time that a breath sample was analyzed. The irrigating fluid bags were weighed to the nearest gram before and after use. Approximately 1000 IU of heparin was added to each collecting bucket to prevent clotting. Special care was taken to avoid spillage of irrigating fluid on the floor. At the end of each 10-min period of each operation, the bladder was emptied, and the irrigating fluid bag and the collecting bucket were changed. The irrigating fluid returns were measured to the nearest 20 mL. Blood loss was calculated as the product of the volume of the irrigating fluid used and the hemoglobin concentration, which was measured with the HemoCue system (HemoCue AB, Ängelholm, Sweden), divided by the existing blood hemoglobin concentration (6). The accuracy of the blood loss measurement was 98%–102%, and the coefficient of variation was <5%, as determined by dispersion of known amounts of blood into irrigating fluid. The volumetric fluid balance was calculated as the difference between irrigating fluid input and output after correction for blood loss (the weight and volume measurements gave the same results) (7).

The blood-hemoglobin concentration, serum sodium (S-Na) and serum potassium (S-K) concentrations, and serum osmolality (S-osmolality) were measured at the end of each 10-min period during TURP, at exactly the same time that a breath sample was taken. The blood-hemoglobin concentration was measured in a Coulter Counter S Plus (Counter Electronics). The S-Na and S-K were analyzed on a Hitachi 737 Automatic Analyser (Hitachi Ltd., Tokyo, Japan). The S-osmolality was determined by freezing-point depression. The coefficients of variation for these analyses were 1.0%, 1.0%, 1.5%, and 1.0%, respectively. Blood-ethanol concentration was analyzed with a Perkin-Elmer headspace gas chromatograph (Perkin-Elmer Corp.), with a standard deviation of 0.01 mg/mL at a mean blood-ethanol concentration of 1.0 mg/mL.

In seven patients, the irrigating fluid consisted of 2.2% glycine in water (without ethanol). A venous cannula was placed in the antecubital vein of both arms. One cannula was used for blood sampling and the other for infusion. When the operation was completed, an intravenous infusion of 0.35 g/kg of ethanol was administered over 20 min. The ethanol was administered as a solution containing 5% glucose and 10% ethanol, using an IVAC 560 infusion pump (IVAC, San Diego, Calif.). Concentrations of ethanol in venous blood and the EB-ethanol concentration were determined at exactly timed 5-min intervals immediately before the infusion started and up to 30 min after it was completed.

The results are presented as mean ± SD or, in the case of skewed distribution, as median and range. Simple and multiple linear regression analysis, repeated measures analysis of variance, the F-test, and the paired Student's *t*-test were used for statistical analysis.

Results

The volumetric fluid balance indicated that irrigating fluid was absorbed in 37 of the 38 patients. Ethanol

Table 1. Operative Data and Blood Chemistry in 37 Patients Undergoing Transurethral Prostatic Resection With Irrigating Fluid Absorption of the Intravascular, Extravascular, Mixed, and Unclassified Types

	Intravascular ($n = 17$)	Extravascular ($n = 5$)	Mixed ($n = 2$)	Unclassified ($n = 13$)
Blood loss (mL)				
Median	356	154	440	116
Range	92–1739	67–1713	189–692	19–742
Operation time (min)	46 ± 22	40 ± 14	35 ± 21	37 ± 17
Weight of resected tissue (g)				
Median	20	17	35	12
Range	7–81	12–53	20–50	5–40
Absorption volume (mL)				
Median	764	879	1576	124
Range	302–2253	423–2246	1055–2097	43–313
Intravenous fluid				
Ringer's solution (mL)	762 ± 354	820 ± 409	712 ± 442	688 ± 373
Dextran 70, 500 mL (n)	5	1	0	0
B-Hb (g/L)				
Before operation	140 ± 8	145 ± 10	146 ± 6	140 ± 15
After operation	123 ± 8	126 ± 14	130 ± 1	129 ± 11
S-Na (mmol/L)				
Before operation	138 ± 2	137 ± 3	138 ± 1	138 ± 2
After operation	133 ± 4	137 ± 2	132 ± 3	137 ± 2
S-K (mmol/L)				
Before operation	4.5 ± 0.4	4.6 ± 0.4	4.1 ± 0.1	4.5 ± 0.4
After operation	4.7 ± 0.5	4.5 ± 0.5	4.6 ± 0.3	4.3 ± 0.4
S-osmolality (mOsm/kg)				
Before operation	296 ± 4	300 ± 11	296 ± 4	296 ± 5
After operation	297 ± 5	297 ± 9	295 ± 3	294 ± 4

B-Hb, blood hemoglobin; S-Na, serum sodium; S-K, serum potassium.
Values are mean ± SD, except where noted.

was detected in the 23 patients with the largest absorption (in 126 of 324 tests of EB).

A comparison between the volumetric fluid balance and EB-ethanol concentration indicated that the lower limit for detection of irrigating fluid absorption with the Alcolmeter was 14 ± 8 mL/min. Patients with absorption below the limit of detection for the ethanol-monitoring method had a coefficient of variation of 0.4% ± 0.2% for S-Na and 0.7% ± 0.3% for S-osmolality. Thus, the baseline for these variables was stable for the 10-min periods when ethanol monitoring indicated that absorption had not taken place.

In 17 patients, there was an increase in the EB-ethanol accompanied by a significant decrease in the S-Na concentration (≥ 2 mmol/L) during the same 10-min period that the volumetric fluid balance indicated that irrigating fluid was being absorbed (Table 1). We interpreted this to indicate that irrigating fluid had been absorbed by the intravascular route (2,4). Figure 2 shows the data obtained in one patient with the intravascular pattern of changes in irrigating fluid absorption. Figure 3A shows the relationship between the EB-ethanol concentration recorded at the end of any 10-min period for all 17 operations and the cumulative volumetric balance during the period of intravascular absorption up to that time. A useful regression equation for estimating the volume of irrigating fluid absorbed from a single measurement of EB-ethanol concentration during TURP (ranging between 0.05 and 0.65 mg/mL) can be obtained by switching the x- and y-axes in Figure 3A, which then yields the following equation:

$$\text{Absorption (mL)} = 2900\ \text{EB-ethanol (mg/mL)}, \qquad (r = 0.71;\ P < 0.001), \quad (1)$$

where EB-ethanol is the concentration of ethanol in exhaled breath.

Figure 3B shows that the prediction of the cumulative absorption from the EB test had a higher precision if EB-ethanol concentration was corrected for absorption time (i.e., the time during which ethanol had been detected in the EB up to that particular measurement of EB-ethanol concentration) (2,4). The correction factor was 0.00864 $\text{mg}\cdot\text{mL}^{-1}\cdot\text{min}^{-1}$, which was obtained from a multiple regression equation relating the cumulative absorption, the EB-ethanol concentration, and the absorption time (mean 24 min; range 10–60) at the end of each 10-min period of TURP. By switching the y- and x-axes in Figure 3B, we obtain the following equation:

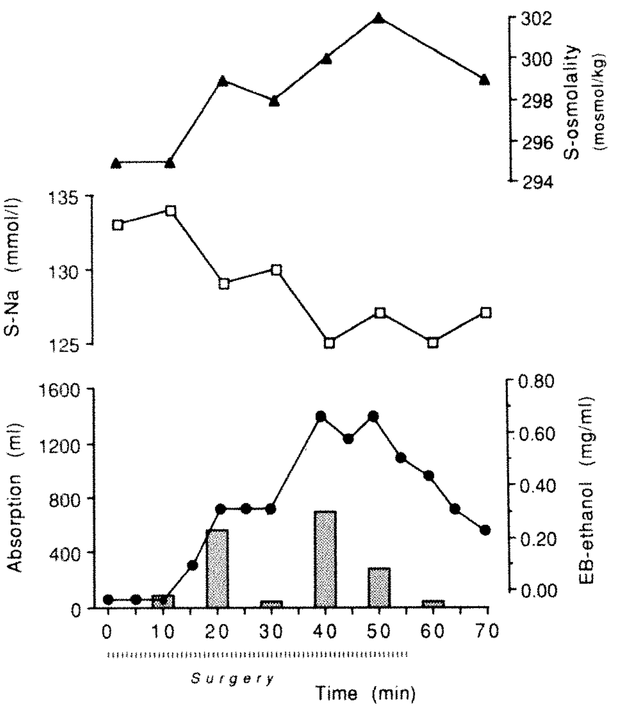

Figure 2. Volume of irrigating fluid absorbed (*bars*), ethanol concentration in expired breath (EB-ethanol), serum osmolality (S-osmolality), and serum sodium concentration (S-Na) measured in one patient with intravascular absorption during transurethral resection of the prostate.

$$\text{Absorption (mL)} = 1828\ \text{EB-ethanol} + 15.8\ t\ (\text{min}) - 81, \qquad (r = 0.89;\ P < 0.001), \quad (2)$$

where t is time. The standard error of an estimate of fluid absorption using Equation (1) was 325 mL; it was 215 mL when using Equation (2) ($P < 0.05$; F-test).

In patients with intravascular absorption, the relationship between the EB-ethanol concentration and the cumulative change in S-Na concentration (maximum −13 mmol/L) up to the end of any 10-min period of TURP was expressed by the following equation:

$$\Delta\text{S-Na (mmol/L)} = 18.1\ \text{EB-ethanol}, \qquad (r = 0.73;\ P < 0.001). \quad (3)$$

The standard error estimate was 2.0 mmol/L. There was an increase in S-osmolality in connection with the largest absorptions (5–10 mOsm/kg when the absorption rate was 50–100 mL/min) (Figure 2).

In five patients, there was only a small increase in EB-ethanol concentration and no significant change in S-Na concentration or S-osmolality in response to irrigating fluid absorption. We interpreted this to indicate that irrigating fluid was absorbed by the extravascular route (2,4). Figure 4 shows the data obtained in one patient with the extravascular pattern of changes in irrigating fluid absorption.

In two patients, our method of analysis suggested that irrigating fluid was absorbed by both the intra-

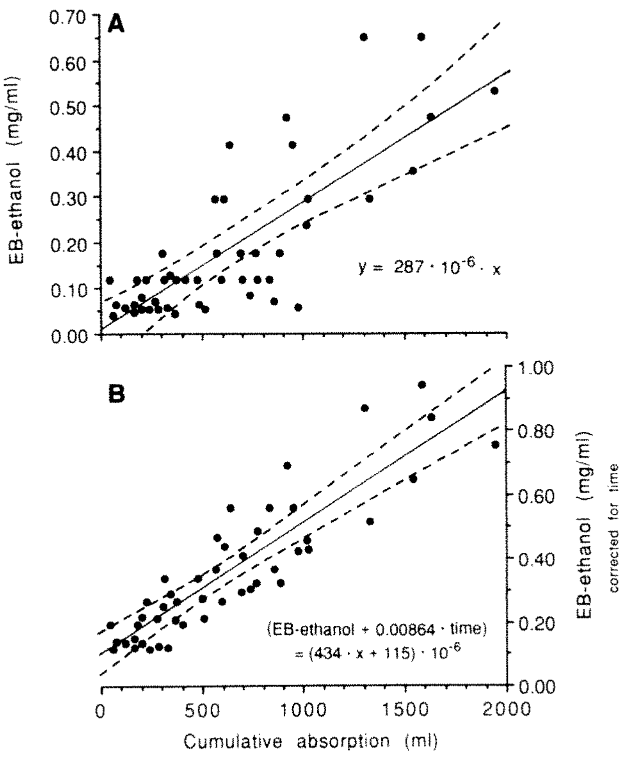

Figure 3. Relationship between the ethanol concentration in the expired breath (EB-ethanol) and the cumulative volumetric fluid balance at the end of all 10-min periods of TURP with intravascular absorption of irrigating fluid (**A**). The same relationship but with EB-ethanol corrected for the time required for absorption to occur (**B**). When absorption time was taken into account, the relationship was strengthened. *Dashed lines* indicate ±1 SD.

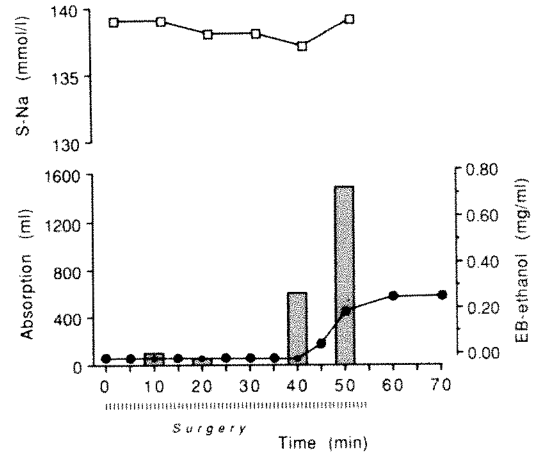

Figure 4. Volume of irrigating fluid absorbed (*bars*), ethanol concentration in the expired breath (EB-ethanol), and serum sodium concentration (S-Na) measured during TURP in one patient with extravascular absorption.

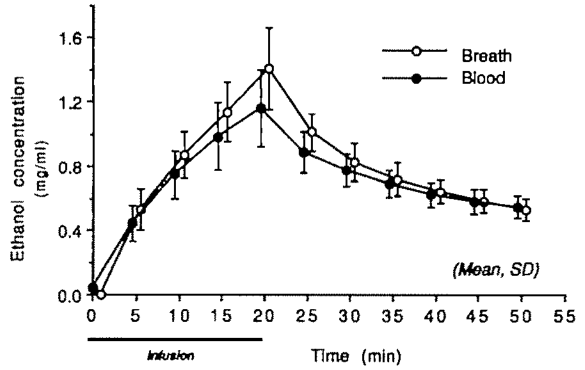

Figure 5. Ethanol concentration in the expired breath and in venous blood during and after an intravenous infusion of 5% glucose and 10% ethanol solution in seven patients.

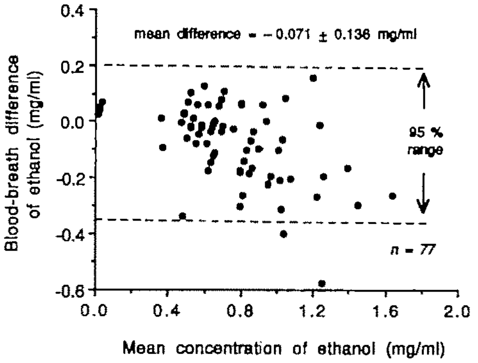

Figure 6. Difference between ethanol concentration in the expired breath and in venous blood in the experiments with intravenous infusion of 5% glucose and 10% ethanol solution in seven patients.

vascular and extravascular routes. However, this occurred during different time periods of each operation.

In 13 patients, the volumetric fluid balance showed that some absorption had taken place without being indicated by the EB test or by a significant decrease in the S-Na concentration ("unclassified absorption") (7). The median absorption rate during the absorption periods was 5 mL/min (range 0.5–18), and the total absorption in these patients was 124 mL (range 43–313). Only one of the 38 patients did not absorb irrigating fluid.

Figure 5 shows the concentration-time profiles of ethanol in venous blood measured both directly and indirectly by analysis of expired air. The average curves are in good agreement (two-factor repeated measures analysis of variance; $P = 0.35$), although the results derived by the analysis of expired air from the endotracheal tube were slightly higher (mean 11%) than the coexisting venous blood level. This difference was significant at 10 ($P < 0.04$), 20 ($P < 0.01$), and 25 min ($P < 0.05$) of the sampling period (paired t-test). The agreement between the blood-ethanol and EB-ethanol concentrations for each paired measurement is displayed in Figure 6.

Discussion

Ethanol monitoring can be used to detect irrigating fluid absorption in TURP surgery. The immediate result obtained from a breath-alcohol test allows early treatment to modify or interrupt absorption by altering the surgical procedure before symptoms ensue (3,8). However, this method was originally developed to monitor fluid absorption in awake patients. In the present study, we examined whether ethanol monitoring is reliable enough for clinical purposes in patients undergoing TURP during general anesthesia. There are two main reasons for suspecting a different accuracy and precision of ethanol monitoring in this situation. The ventilation/perfusion ratio is altered by general anesthesia (9), which may interfere with the blood/breath partition coefficient of ethanol. Moreover, the measurement of EB-ethanol may be influenced by the addition of fresh gas flow in close proximity to the connection between the endotracheal tube and the breathing circuit (Figure 1).

Our results show that the precision of ethanol monitoring in patients undergoing TURP during inhaled anesthesia is almost identical to that for awake patients (2). There was a linear correlation between the EB-ethanol concentration and absorption volumes up to 1950 mL at all times during TURP (Figure 3). The standard error estimate of the volume of irrigating fluid absorbed by the use of a single EB-ethanol concentration value was slightly >300 mL (Equation [1]). This error became significantly smaller by correcting EB-ethanol concentration for absorption time. The absorption time is important, because EB-ethanol concentration is appreciably higher during rapid absorption. This can be understood from the nonequilibrium of ethanol between central and peripheral compartments. Furthermore, the lowering effect of alcohol oxidation on EB-ethanol concentration is greater during prolonged absorption. Whereas Equation (1) reflects the average absorption time in the study, Equation (2) takes into account this variable for each prediction of fluid absorption. The EB-ethanol concentration attains a higher value when the absorption time is longer, according to a constant (correction factor) that carries both distributional and eliminational information for ethanol. The constant can be obtained directly from Equation (2) as 15.8 divided by 1828, which is 0.00864, or 1/116 $\text{mg}\cdot\text{mL}^{-1}\cdot\text{min}^{-1}$. In previous studies in awake patients, this constant was 1/117 (4) and 1/142 (2).

The measurements of ethanol concentration in breath and blood (Figure 5) and a comparison among

Equations (1)–(3) and the corresponding regression equations previously obtained in awake patients (2) suggest that the breath test regularly shows slightly higher values than expected during inhaled anesthesia. This can probably be explained by less reabsorption of alcohol in the oral cavity during expiration, because the endotracheal tube prevents contact between the alcohol and the mucosa.

Hultén et al. (5) have reported reasonably good correlation between EB-ethanol concentration and other methods of measuring absorption, but they did not reach a firm conclusion about the precision of ethanol monitoring in patients undergoing TURP with general anesthesia (5). These workers did not use inhaled anesthetics, which is the most common form of general anesthesia for TURP in our hospital.

The most common pattern of changes in connection with absorption consists of an increase in EB-ethanol concentration and a decrease in S-Na concentration within the same 10-min period that the absorption occurs. Such a rapid response suggests absorption through severed prostatic veins (intravascular absorption). In these patients, the S-Na level remained stable when absorption did not occur and during absorption it could be followed approximately through the EB-ethanol measurement (Equation [3]). A total absorption of 1 L (breath alcohol ≈0.25 mg/mL) should initiate prompt action to reduce further absorption, because this amount may result in mild symptoms of the "TUR syndrome" (2,3). Such actions include reduction of the fluid pressure, thorough hemostasis, or termination of the resection (3,5,8).

There are several other patterns of changes in EB-ethanol and S-Na concentrations after irrigating fluid absorption (Table 1), but only the extravascular type is of importance to the clinician (1). Ethanol monitoring does detect extravascular absorption, but the ethanol levels are lower and increase more slowly than when the same amount of irrigant is absorbed into the circulation. Furthermore, the maximal EB-ethanol level persists when absorption has stopped (Figure 4). The following test can usually determine whether the fluid enters the body by the intravascular or extravascular route. If ethanol is detected in the EB, the operation is stopped for 5 min, and one repeat analysis of the exhaled air is made. If absorption was intravascular, the second result will be less than the first but will remain unchanged or even be higher if absorption was extravascular (10).

In conclusion, we found that ethanol monitoring in tracheally intubated patients undergoing TURP during inhaled anesthesia is precise enough to allow detection of absorption of irrigating fluid in amounts that may be clinically important for the safety of the patient.

Nurse anesthetist Annika Nordin and Dr. Catherine Hannaford assisted in obtaining the data.

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Tyraminelike Action of Succinylcholine in the Isolated, Blood-Perfused Canine Atrium

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The mechanisms of succinylcholine-induced cardiac effects have not been fully elucidated. Accordingly, we studied the effects of succinylcholine on atrial rate and contractile force in the isolated canine atrium perfused with donor blood. The sinus node artery was perfused with heparinized blood from the common carotid artery of the donor dog at a constant pressure of 100 mm Hg. When succinylcholine in a dose range of 30–1000 μg was injected directly into the sinus node artery of the isolated atrium, increases in atrial rate and contractile force were observed in a dose-related manner. The atrial rate and contractile force were increased to 10.5% ± 1.8% (mean ± SEM) and 56.8% ± 8.5% above the control values after the administration of 1000 μg of succinylcholine, respectively. After treatment with propranolol, the positive chronotropic and inotropic effects of succinylcholine and norepinephrine were significantly suppressed. Hexamethonium or tetrodotoxin pretreatment inhibited the cardiac effects of nicotine but did not modify the succinylcholine-induced cardiac effects. The succinylcholine-induced effects were significantly inhibited by treatment with imipramine, which also suppressed the tyramine-induced effects. We conclude that succinylcholine has cardioexcitatory properties mediated by release of catecholamine due to a tyraminelike action.

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Succinylcholine is a depolarizing muscle relaxant having both rapid onset and very short duration of action; however, there are many conflicting reports with reference to the effects of succinylcholine on the cardiovascular system. Clinically, hypertension and hypotension, tachycardia, and bradycardia are seen during continuous infusion or repeated intravenous injection of succinylcholine (1–3). In experimental studies, succinylcholine produces a dual cardiac action (i.e., a negative chronotropic effect at small doses and a positive one at large doses) in the isolated heart (4). Several mechanisms by which succinylcholine exerts its cardiac effects have been postulated: (a) blockade of cardiac synapses (5); (b) stimulation of the afferent vagal receptors (6); (c) stimulation of autonomic ganglia and mobilization of epinephrine (7); (d) stimulation of nicotinic receptors at the sympathetic nerve terminals (8); and (e) interaction with cholinergic receptors resulting in release of catecholamines (9).

In 1982, Yasuda et al. (10) found that 30–1000 μg of succinylcholine injected into the sinus node artery of the intact dog induced a transient dose-related positive chronotropic effect that was inhibited by pretreatment with reserpine or a β-adrenergic blocker, pindolol. From their findings, we presume that succinylcholine probably liberates a catecholamine by either a nicotinelike or tyraminelike action, because both actions are blocked by treatment with reserpine, which depletes a catecholamine from sympathetic nerve endings (11).

In the present study, we have observed the effects of succinylcholine on pacemaker activity and myocardial contractility in isolated, blood-perfused canine atrial preparations (12,13). Furthermore, to clarify the mechanism underlying succinylcholine-induced catecholamine release, we examined whether the cardiac responses to succinylcholine were modified by sympathetic blocking drugs (i.e., propranolol, hexamethonium [C6], tetrodotoxin [TTX], and imipramine). It is established that a nicotinelike effect is inhibited by C6 (12,14) or TTX (15,16), whereas a tyraminelike effect is suppressed by imipramine (17).

Methods

This study was approved by our institutional Animal Care and Use Committee. Twenty-eight donor dogs weighing 9–19 kg were anesthetized with 30 mg/kg of

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intravenous pentobarbital and mechanically ventilated with an inspired O_2 concentration of 0.2. Heparin (500 *USP* U/kg IV) was administered at the beginning of the perfusion, and 200 *USP* U/kg was added at 1-h intervals. The systemic arterial blood pressure of the donor dog was measured from the cannulated right femoral artery with a pressure transducer, and heart rate was measured with a cardiotachograph triggered by the R wave of electrocardiographic lead II.

Isolated right atrial preparations were obtained from 28 other mongrel dogs weighing 7–16 kg and anesthetized with pentobarbital (30 mg/kg IV). After treatment with 200 *USP* U/kg of intravenous sodium heparin, the right atrium was excised and plunged into a cold Tyrode's solution at 4–10°C. The mean wet weight of the atrial preparation was 7.9 g ($n = 28$). The sinus node artery was cannulated via the right coronary artery and perfused with heparinized blood from the common carotid artery of the donor dog by means of a peristaltic pump (Harvard Apparatus, model 1210). A pneumatic resistance was placed in parallel with the perfusion system so that the perfusion pressure could be maintained constant at 100 mm Hg. Blood flow to the isolated atrium was 3–9 mL/min.

The ventricular margin of the isolated atrium was fixed to a stainless steel bar and placed in a cup-shaped glass container maintained at 37°C. The atrium was stretched to a resting tension of 2 g. The isometric tension was recorded on a thermowriting rectigraph (Nihon Kohden, WT 685G). A pair of silver electrodes, with an interelectrode distance of 1.5 mm, were brought into contact with the epicardial surface of the isolated atrium to record the electrogram. The atrial rate was derived from the atrial electrogram with a cardiotachometer. Details of this preparation have been described previously (12,13).

We performed two series of experiments. In the first series, we observed the effects of succinylcholine in doses ranging from 30 to 1000 μg on the sinoatrial pacemaker activity and atrial contractility in six isolated atria. In the second series, we examined whether the cardiac responses to succinylcholine at a dose of 1000 μg were modified by sympathetic blocking drugs: (a) a β-adrenergic blocker, propranolol, in five experiments using five isolated atria; (b) an antagonist of nicotinic receptors, C6, in four experiments using four isolated atria; (c) a fast, inward sodium channel blocker, TTX, in four experiments using four isolated atria; and (d) a neuronal uptake_1 blocker, imipramine, in five experiments using five isolated atrial preparations. Furthermore, we tested whether the cardiac responses to succinylcholine at the smallest dose of 30 μg were inhibited by propranolol or imipramine in two experiments using two isolated atria. To rule out a skew result, the order of drug injection was randomized.

The following drugs were used: succinylcholine chloride (Kyorin Pharmaceutical Co., Tokyo, Japan); *d,l*-norepinephrine hydrochloride (NE) (Sankyo, Tokyo, Japan); *d,l*-propranolol hydrochloride (Sigma Chemical Co., St. Louis, Mo.); nicotine (base) and hexamethonium bromide (C6) (Yamanouchi, Tokyo, Japan); tetrodotoxin (TTX) (Sankyo); tyramine hydrochloride (Wako Purechemical Industries, Osaka, Japan); and imipramine hydrochloride (Fujisawa, Osaka, Japan). Each drug was dissolved in physiologic saline solution before starting the experiment. Drugs were injected into the sinus node artery of the isolated atrium through a rubber tube with a microsyringe (Terumo Co.). The amount of drug solution injected with the microsyringe was 0.01–0.03 mL over a period of 4 s. There were no changes in atrial rate and contractile force when 0.01–0.03 mL of physiologic saline solution was injected into the sinus node artery over a period of 4 s.

Data are given as percentage changes in a maximal positive or negative direction. Data collected before and after treatment with a drug were analyzed by paired *t*-tests; $P < 0.05$ was accepted as indicating a significant difference.

Results

Effects of Succinylcholine on Sinoatrial Nodal Pacemaker Activity and Atrial Contractility

When succinylcholine in doses ranging from 30 to 1000 μg was injected directly into the cannulated sinus node artery of the isolated atrium, positive chronotropic and inotropic responses were induced in a dose-related manner. Figure 1 shows the dose-response curves for the chronotropic and inotropic responses to succinylcholine in six isolated atria. The threshold dose for inducing positive cardiac effects was 10–30 μg in the six preparations. A dose of 30 μg injected into the sinus node artery is considered to be comparable to that achieved at the level of the sinoatrial node after a standard clinical intravenous dose (10). Succinylcholine at a dose of 1000 μg produced conspicuous positive chronotropic and inotropic responses.

Effects of Propranolol on Positive Cardiac Responses to Succinylcholine

These experiments were carried out to confirm that the positive cardiac effects of succinylcholine were mediated through β-adrenergic receptor stimulation by release of norepinephrine from the sympathetic nerve endings. The positive chronotropic and inotro-

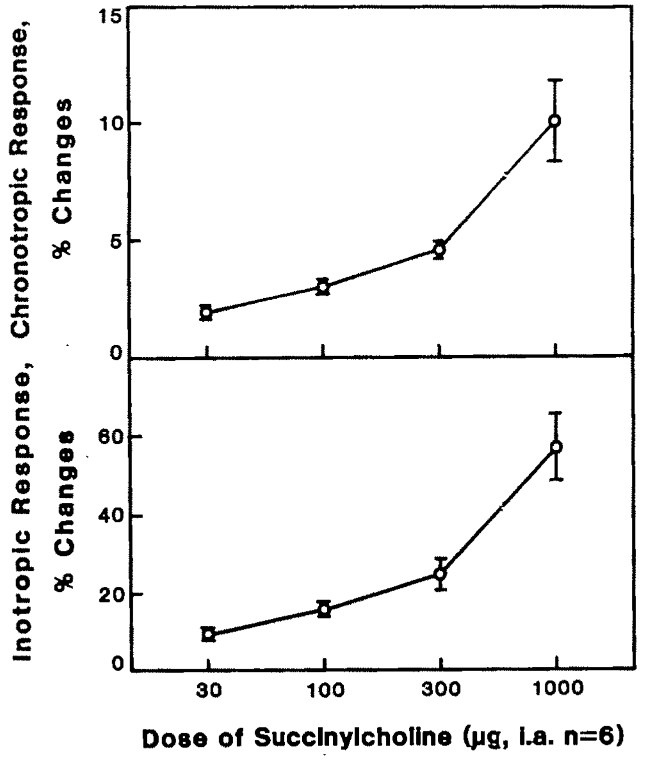

Figure 1. Dose-response curves as percentage changes in the maximal positive chronotropic (*upper panel*) and inotropic (*lower panel*) responses to succinylcholine. *Points* represent means and *vertical lines* show SEM. Baseline levels of atrial rate and contractile force in six isolated atria (i.a.) were 114 ± 6 (mean ± SEM) beats/min and 2.7 ± 0.3 g, respectively.

pic responses to succinylcholine were suppressed by pretreatment with a β-adrenoceptor blocker, propranolol, which markedly blunted norepinephrine-induced positive chronotropic and inotropic responses (Figure 2). Propranolol by itself caused negative cardiac effects. Each agonist was administered after atrial rate and contractility had reached steady state. The blocking effect of propranolol continued over 30 min. Data summarizing five experiments are shown in Figure 3. Propranolol (3 μg) significantly ($P < 0.01$) suppressed the positive chronotropic and inotropic responses to 1000 μg of succinylcholine and 0.03 μg of norepinephrine. The same dose of propranolol completely inhibited the positive chronotropic and inotropic responses to succinylcholine at the lowest dose of 30 μg in two experiments (data not shown).

Effects of Hexamethonium and Tetrodotoxin on Positive Cardiac Responses to Succinylcholine

We tried to elucidate whether succinylcholine-induced norepinephrine release was attributed to a nicotinic action. Nicotine (3 μg) produced negative chronotropic and inotropic responses (13.0% ± 3.1% and 56.7% ± 12.2% decrease, respectively), followed quickly by positive chronotropic and inotropic responses (36.4% ± 10.0% and 157.1% ± 38.3% increase, respectively) in four isolated atria. The duration of action of nicotine was from 1 to 2 min. At a dose of 300 μg, C6 significantly ($P < 0.05$) inhibited the responses to nicotine; that is, after C6 treatment, nicotine (3 μg) induced negative chronotropic and inotropic responses (1.8% ± 0.5% and 4.8% ± 1.7% decrease, respectively), followed by positive chronotropic and inotropic responses (1.9% ± 0.8% and 16.8% ± 8.1% increase, respectively) in the four isolated atria. With the same dose, C6 did not modify the responses to succinylcholine; that is, 1000 μg of succinylcholine produced positive chronotropic and inotropic responses (6.3% ± 1.1% and 61.5% ± 14.1% increase; $n = 4$) before C6 and (6.7% ± 1.2% and 59.7% ± 15.7% increase; $n = 4$) after C6, respectively. After 3 μg of TTX, the responses to nicotine were also significantly ($P < 0.05$) suppressed: nicotine (3 μg) produced negative chronotropic and inotropic responses (31.5% ± 9.6% and 41.6% ± 13.4% decrease; $n = 4$), followed by positive chronotropic and inotropic responses (18.0% ± 3.0% and 143.0% ± 34.3% increase; $n = 4$) before TTX and 4.1% ± 2.8% and 12.1% ± 5.4% decrease ($n = 4$), followed by 1.7% ± 0.4% and 17.5% ± 5.5% increase ($n = 4$) after TTX, respectively. On the other hand, succinylcholine-induced responses were not affected by 3 μg of TTX: 1000 μg of succinylcholine induced positive chronotropic and inotropic responses (5.2% ± 0.9% and 78.4% ± 10.5% increase; $n = 4$) before TTX and (5.2% ± 0.5% and 80.3% ± 12.7% increase; $n = 4$) after TTX, respectively.

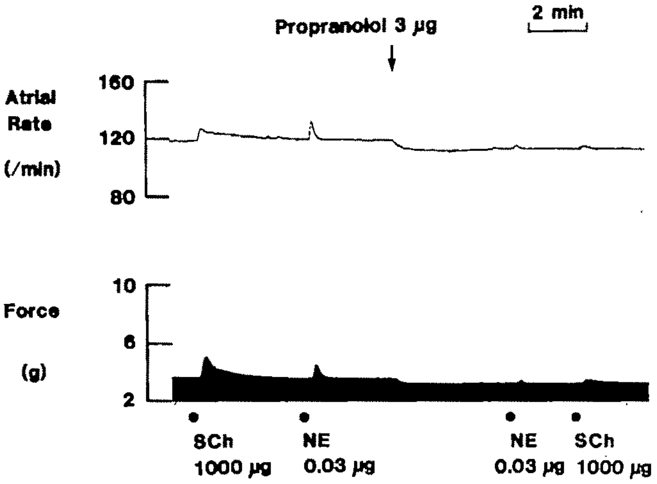

Figure 2. Effects of propranolol on responses of atrial rate and contractile force to succinylcholine (SCh) and norepinephrine (NE) in an isolated, blood-perfused canine atrium.

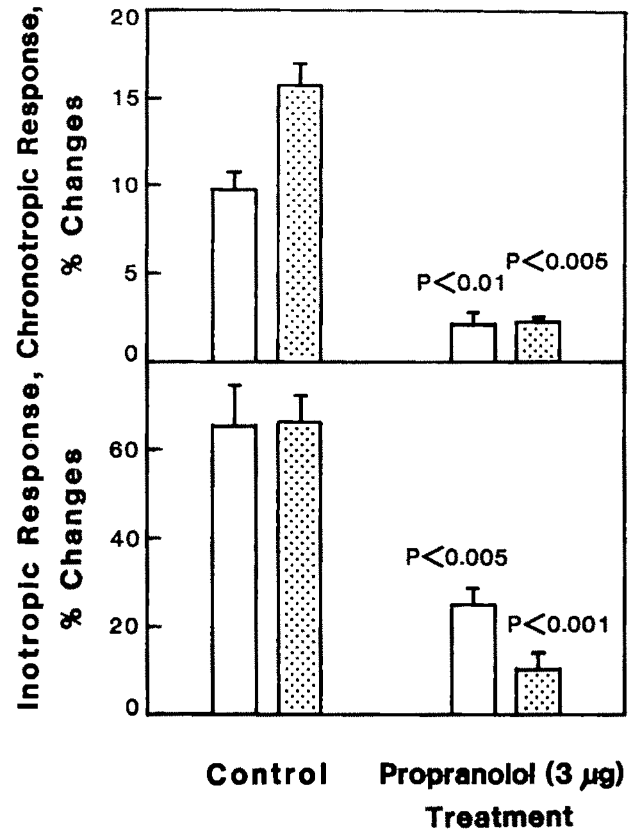

Figure 3. Effects of 3 μg of propranolol on the percentage changes in chronotropic and inotropic responses to 1000 μg of succinylcholine (SCh, *open bars*) and 0.03 μg of norepinephrine (NE, *stippled bars*) in five isolated atria. *Vertical lines* show SEM. Comparisons are with control values (paired *t*-test). Baseline levels of atrial rate and contractile force in five atria were 113 ± 7 beats/min (mean ± SEM) and 2.4 ± 0.4 g, respectively.

Effects of Imipramine on Positive Cardiac Responses to Succinylcholine

We attempted to determine whether succinylcholine-induced norepinephrine release was due to a tyraminelike action. Figure 4 shows typical effects of imipramine, a drug that inhibits the neuronal uptake$_1$ mechanism, on responses to succinylcholine, tyramine, and norepinephrine. Imipramine by itself induced negative chronotropic and inotropic effects followed by positive effects. The effects of each agonist were examined in the subsequent steady state. The positive chronotropic and inotropic responses to succinylcholine and tyramine were suppressed by treatment with imipramine, whereas the positive responses to norepinephrine were enhanced but not significantly. The results of these five experiments are summarized in Figure 5. Imipramine (300 μg) significantly ($P <$ 0.01) suppressed the positive chronotropic and inotropic responses to 1000 μg of succinylcholine and 3 μg of tyramine. Imipramine (300 μg), as well as propranolol, completely inhibited the positive responses to succinylcholine at the lowest dose of 30 μg in two experiments (data not shown).

Discussion

Many conflicting reports still exist concerning the cardiovascular effects of succinylcholine in laboratory animals and in humans. Beretervide (18) reported that intravenous injections of succinylcholine in conscious rabbits caused a decrease in arterial blood pressure and bradycardia at a relatively small dose and a large increase in arterial blood pressure at a large dose (0.4 mg/kg). Williams et al. (3) reported that hypertension and tachycardia after injections of succinylcholine occurred in patients anesthetized with several anesthetics, whereas bradycardia and prolonged asystole were induced by the administration of successive doses of succinylcholine in patients receiving cyclopropane or halothane. One year later, Galindo and Davis (19) described hypertension and tachycardia after administration of a large dose of succinylcholine in rhesus *Macacus* monkeys. More recently, Hannallah et al. (20) stated that intramuscular injections of succinylcholine showed a transient increase followed by a decrease in heart rate in children anesthetized with N_2O/O_2 and halothane. In isolated rabbit heart, succinylcholine produced a dual action (i.e., a negative chronotropic effect at small doses and a positive one at large doses) (4).

In the present study, succinylcholine injected directly into the sinus node artery of the isolated canine atrium had dose-related positive chronotropic and inotropic effects and did not have any negative effects. Schoenstadt and Whitcher (21) suggested that hexaflorenium slowed the hydrolysis of succinylcholine to succinylmonocholine and choline and prevented the succinylcholine-induced bradycardia. Succinylmonocholine causes a negative chronotropic effect attributed to a muscarinic action on the sinoatrial node (10,22). Therefore, bradycardia seen after succinylcholine administration may not be due to the action of succinylcholine itself but, rather, to that of its metabolic products.

Yasuda et al. (10) found that 30–1000 μg of succinylcholine injected into the sinus node artery of the intact dog caused a transient dose-related positive chronotropic effect that was suppressed by pretreatment with reserpine or a β-adrenergic blocker, pindolol. Their findings indicate that succinylcholine probably liberates a catecholamine by either a nicotinelike or tyraminelike action, because both actions are blocked by reserpine, which depletes catecholamine from sympathetic nerve endings (11). Accordingly, we attempted to determine which of these actions is responsible for the liberation of catecholamine after succinylcholine administration.

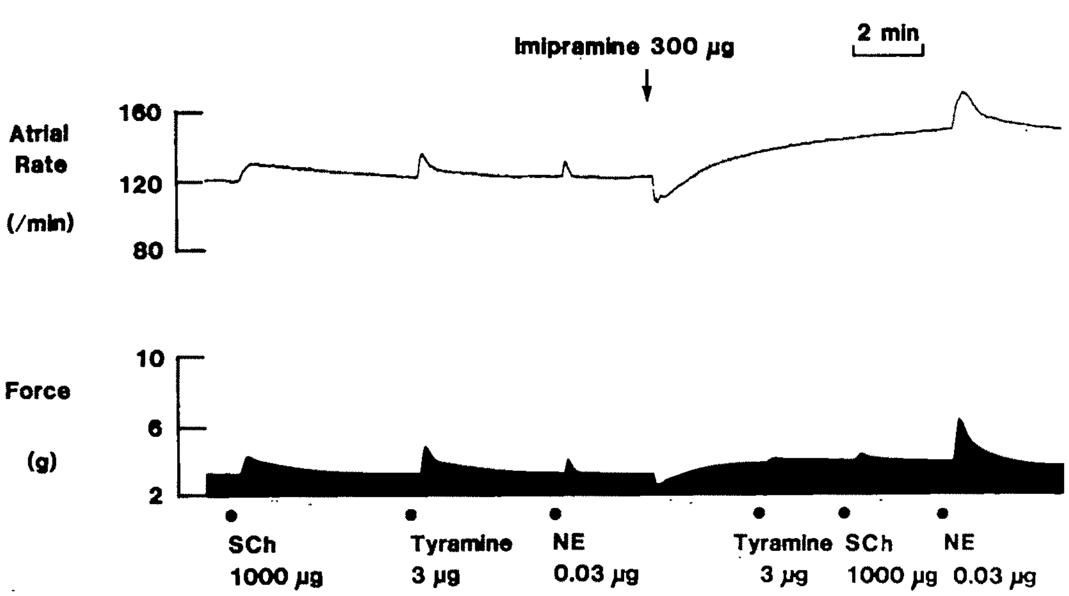

Figure 4. Effects of imipramine on atrial rate and contractile force responses to succinylcholine (SCh), tyramine, and norepinephrine (NE) in an isolated, blood-perfused canine atrium.

In 1983, Nigrovic et al. (8) reported that plasma norepinephrine levels increased significantly 2 min after the injection of succinylcholine in anesthetized and manually ventilated patients. They postulated that succinylcholine might stimulate nicotinic receptors on the postganglionic adrenergic nerve endings. Stimulation of nicotinic receptors in the sympathetic endings results in nerve excitation, which causes the liberation of norepinephrine. It is also an accepted fact that C6 blocks nicotinic receptors not only at parasympathetic ganglia but also at sympathetic nerve terminals (12,14). In our study, the negative chronotropic and inotropic responses followed by positive responses to nicotine were significantly inhibited by treatment with C6, whereas the responses to succinylcholine were not influenced by C6. The succinylcholine-induced responses were also not affected by use of TTX, which blocks nerve excitation in the autonomic nervous system (15,16). On the other hand, the cardiac responses to nicotine were suppressed by TTX. Moreover, we have observed no negative components in the cardiac responses to succinylcholine even after propranolol (Figures 2 and 3). Although a few investigators could not observe the biphasic cardiac responses after exposure of atria to nicotine (23–25), it consistently produces negative chronotropic and inotropic responses as well as positive ones in the isolated, blood-perfused canine atria, as reported previously (26–28). From these findings, the positive cardiac effects of succinylcholine are probably not due to a nicotinic action in the isolated atrium.

In this study, the tyramine-induced positive chronotropic and inotropic responses were significantly inhibited by treatment with imipramine, which po-

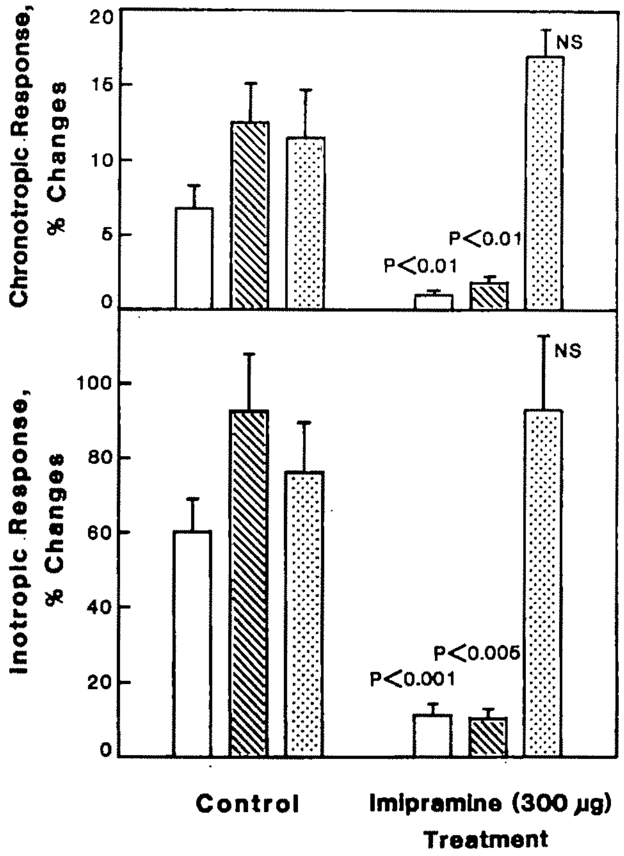

Figure 5. Effects of 300 µg of imipramine on the percentage changes in chronotropic and inotropic responses to 1000 µg of succinylcholine (SCh, *open bars*), 3 µg of tyramine (*hatched bars*), and 0.03 µg of norepinephrine (NE, *stippled bars*) in five isolated atria. *Vertical lines* show SEM. Comparisons are with control values (paired *t*-test); NS, no statistical significance ($P > 0.05$). Baseline levels of atrial rate and contractile force in five atria were 110 ± 7 beats/min (mean ± SEM) and 2.5 ± 0.3 g, respectively.

tently blocks the uptake$_1$ mechanism (17), but not the uptake$_2$ mechanism (29), in the adrenergic nerve terminals. It has been postulated that the norepinephrine efflux evoked by tyramine represents the final result of a number of processes, such as accumulation of tyramine by the uptake$_1$ mechanism, metabolism in the cytoplasm, vesicular uptake, conversion to octopamine and displacement of norepinephrine, outward transport of norepinephrine, and diffusion through the adventitia and media (30–32). Similar to those of tyramine, the succinylcholine-induced positive chronotropic and inotropic responses were significantly suppressed by imipramine. It is recognized that a nicotinelike action is susceptible to TTX but a tyraminelike action is resistant to TTX (33,34). Thus, we conclude that succinylcholine liberates catecholamine by a tyraminelike action.

The nicotinic action of succinylcholine, similar to that of acetylcholine, has been adequately described in previous reports (3,7,8,18,19); however, we demonstrated that the action of succinylcholine on the sympathetic nerve endings is similar to tyramine and different from nicotine in the isolated canine atrium.

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Direct Measurement of Nitrous Oxide MAC and Neurologic Monitoring in Rats During Anesthesia Under Hyperbaric Conditions

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The minimum alveolar concentration (MAC) of nitrous oxide necessary to prevent purposeful movement in rats has not been directly measured; rather, it has been extrapolated because the required partial pressure exceeds 760 mm Hg, or 1 atm absolute pressure (ATA). Values reported have ranged from 1.36 to 2.20 ATA (136–220 vol%, or 1034–1672 mm Hg). By maintaining general anesthesia at 2.25 ATA (1710 mm Hg), we directly measured the nitrous oxide MAC in 17 Long-Evans rats during mechanical ventilation and monitoring of two-channel electroencephalogram, compressed spectral array and cortical evoked potentials, electrocardiograph, and respiratory and anesthetic gases by mass spectrometry. After a minimal stabilization period of 30 min during ventilation by 1.8 ATA nitrous oxide and 0.45 ATA oxygen, MAC measurements were begun. Each rat was given up to three noxious electrical stimulations of 50 V by 10-ms-duration pulses at 50/s for 45 s. The partial pressure of nitrous oxide was decreased by approximately 10% after each negative response. The MAC was taken as the nitrous oxide concentration midway between that at which there was no response and that at which the rat moved purposefully. The nitrous oxide MAC in Long-Evans rats was determined to be 1.55 ± 0.16 ATA (mean ± SD). Hyperbaric nitrous oxide decreased electroencephalogram wave frequency to a predominantly theta rhythm of increased amplitude. Cortical evoked potentials had decreased wave amplitudes and increased latencies with increasing partial pressures >0.75 ATA. General anesthesia with nitrous oxide at hyperbaric pressures allows direct measurement of the nitrous oxide MAC in rats and demonstrates neurophysiologic depressant effects on the electroencephalogram and somatosensory evoked potentials.

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The minimum alveolar concentration (MAC) of nitrous oxide (N_2O) necessary to prevent repetitive, purposeful movements in rats has not been directly measured. The N_2O MAC is a partial pressure value >760 mm Hg, or 1 atm absolute pressure (ATA); hyperbaric exposure is required for MAC measurement and to enable investigators to ventilate animals with high enough N_2O partial pressures to exceed MAC as well as prevent hypoxemia. Although the MAC of N_2O has been directly measured and reported to be 1.04 ATA in humans (1), the reported values for N_2O MAC in rats have been primarily extrapolated from the presumed linear additivity between N_2O and volatile anesthetics and the correlation of anesthetic potency with lipid solubility (2,3). Values reported have ranged from 1.36 to 2.20 ATA. However, nonlinear additivity of N_2O and other anesthetics has also been reported (3–5). Wardley-Smith and Halsey (6) found N_2O potency to be 1.48 ± 0.076 ATA (mean ± SD) in an unknown number of rats after 10-V electrical stimulation to the tail. Recent theories of anesthetic action have also postulated that there is anesthetic binding to specific membrane proteins (perhaps some degree of anesthetic-specific proteins) rather than disruption of cell membrane lipids (7). Although these theories may be formulative and not fully proved, the extrapolated values assigned to MAC based on lipid solubility or linear additivity because of the same mechanism of action in rats can be questioned. Because of the importance of knowing the true value for N_2O MAC in rats, in particular for experiments in which anesthetic potency and relative dosages of anesthetics are an important part of the protocol, we determined to

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directly measure the MAC of N_2O in rats during general anesthesia in a hyperbaric chamber.

Methods

After approval by the Pennsylvania State University College of Medicine Animal Utilization Committee, we studied 17 Long-Evans rats of similar ages (~10 wk) and weights (370 ± 69 g) to directly measure the MAC of N_2O. All rats were fed a similar unrestricted diet of Purina Rat Chow. All studies were performed between 8 AM and 4 PM.

Anesthesia was induced in a 2-L plexiglass box with a total gas flow of 2 L/min of oxygen with 4.0% isoflurane. Each rat was orotracheally intubated and mechanically ventilated with a small-animal volume ventilator (Harvard Apparatus, Cambridge, Mass.) to mild hypocapnea. Each animal was monitored by compressed spectral array with two-channel electroencephalogram (EEG) and somatosensory cortical evoked potentials (Neurotrac, Interspec Medical, Conshohocken, Pa.), electrocardiograph, and respiratory gas measurements, including inspired oxygen, end-tidal carbon dioxide, N_2O, and isoflurane by a calibrated, accurate mass spectrometer (MGA 1100, Marquette Gas Monitoring Corp, St. Louis, Mo.) (8). Each animal was placed on a heating blanket for maintenance of body temperature stability. Temperature did not vary by >1°C during the experiment.

All equipment was positioned inside an animal hyperbaric chamber (Reimers Engineering, Alexandria, Va.). Isoflurane was discontinued from the ventilating gas and flushed from the respiratory circuit. The chamber was sealed and chamber pressure increased to 2.25 ATA (1710 mm Hg). After reaching stable pressure, ventilation was continued with 1.8 ATA N_2O and 0.45 ATA O_2.

The cortically recorded somatosensory evoked potentials (CEPs), two-channel analogue EEG, and compressed spectral array were recorded constantly throughout the experiment. Needle electrode impedance was maintained at <5000 Ω. The evoked-potential stimulator intensity was adjusted to consistently elicit a twitch from the distal paw of the lower limb. A stimulus rate of 5/s with 256 repetitions and an analysis time of 200 ms after each stimulus was utilized. Cortical responses from the peripheral hindlimb stimulation were recorded from contralateral scalp electrodes. The animals were constantly observed by an investigator through a chamber porthole.

After a minimal stabilization period of 30 min and end-tidal isoflurane approaching 0 (maximal detected end-tidal isoflurane was 0.03%), testing for MAC was begun using a supramaximal electrical stimulation technique (9,10). The stimulus used was defined as supramaximal, because electrical stimulation of higher voltage or longer duration has not been shown to result in a response in tested animals (10). Each rat received an electrical stimulation of 50 V by 10-ms-duration pulses at 50/s for 45 s by a Grass SD-5 stimulator. The stimulus was applied subcutaneously to the lower abdomen from a single-needle electrode. The partial pressure of N_2O was decreased by approximately 10% if there was a negative response for three periods of stimulation. A positive response was taken as repetitive, purposeful movement. This did not include tail-wagging activity, back arching, or maintained limb extension. A minimal 15-min equilibration time was taken between each change and stable end-tidal N_2O maintenance documentation. The MAC was taken as the expired N_2O partial pressure in ATA midway between that at which there was no response and that at which the rat moved purposefully.

Although electrical stimulation has often been utilized as a noxious stimulus for MAC measurement, electrical stimulation was compared with the full-ratchet tail-clamp technique in three Sprague-Dawley rats for the measurement of the MAC of isoflurane. Both noxious stimuli were applied after each decrease in end-tidal isoflurane, beginning at 1.6%.

The mean value of the determined MAC values (±SD) was taken as the MAC of N_2O for Long-Evans rats and the MAC of isoflurane for Sprague-Dawley rats.

Results

The directly measured MAC of N_2O in Long-Evans rats was found to be 1.55 ± 0.16 ATA. The range of measured N_2O MAC values was from 1.38 to 1.74 ATA. Positive responses could be elicited repeatedly. The MAC of isoflurane in the three rats tested was the same, 1.31% ± 0.08%, when determined by both electrical stimulation and tail-clamping.

During the study, end-tidal CO_2 was maintained at >25 mm Hg and did not exceed 45 mm Hg in all animals. Normoxic gas mixtures were delivered to all animals throughout the study.

Nitrous oxide was found to be a neurophysiologic depressant both through absence of responses to electrical stimulation and through decreased neuroelectrical activity as monitored by EEG. The analogue EEG output of the computerized EEG showed decreased fast-wave activity with increasing N_2O partial pressure; there was a preponderance of slow-wave activity at >0.90 ATA N_2O (Figure 1). Low-amplitude (<20 μV), beta wave activity was predominant below 0.65 ATA N_2O. Amplitude increased and electrical

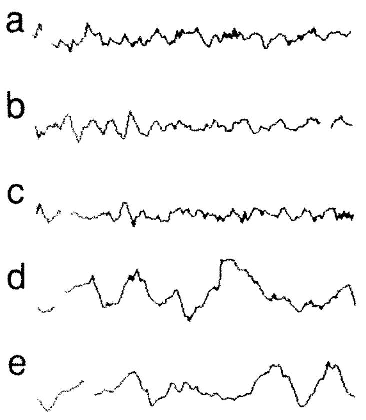

Figure 1. Two-channel EEG was recorded in rats during hyperbaric exposure to N_2O and O_2 at 2.25 ATA (atmospheres absolute pressure). Increased N_2O partial pressures decreased EEG frequency and increased waveform amplitude. End-tidal N_2O measurements correlating with each raw EEG recording were *a*, 0%; *b*, 31% (0.31 ATA); *c*, 68% (0.68 ATA); *d*, 118% (1.18 ATA); *e*, 164% (1.64 ATA).

Table 1. Effects of N_2O on the Electroencephalogram in Rats

N_2O (ATA)	Predominant frequency[a]	Amplitude[b]
0	Beta	Low
0.40–0.65	Beta	Low
0.70–0.80	Alpha	Medium
0.90–1.0	Alpha	High
1.05–1.45	Alpha–theta	Medium–high
1.50–1.60	Theta	Medium–high
1.65–1.90	Theta	Medium–high

ATA, 1 atm absolute pressure.
[a] Alpha, 8–13 Hz; beta, >13 Hz; delta, 0–3 Hz; theta, 4–7 Hz.
[b] Low, <20 μV; medium, 20–50 μV; high, >50 μV.

activity decreased as N_2O partial pressure increased (Table 1).

Neuroelectrical depression was also noted in the CEP recordings. The latency of the CEP was less affected than the amplitude. Although the trends in CEP changes were similar across the population studied, individual examples best exemplify changes at specific N_2O partial pressures (Figure 2). Amplitude decreased with each increase in N_2O partial pressure. Latency was relatively stable until N_2O concentration exceeded approximately 0.75 ATA (Table 2). During ventilation with N_2O >0.9 ATA, the CEP waveform was altered in some animals to the extent that amplitude and latency could not be accurately measured.

No difficulties were encountered with the stimulating electrodes. Tissue burns were not encountered at the stimulating or recording sites.

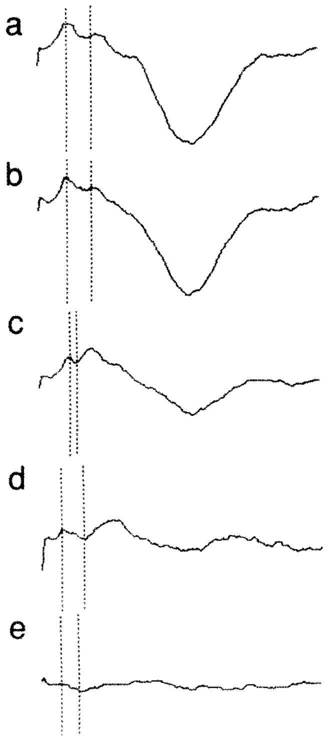

Figure 2. Somatosensory evoked potentials were cortically recorded after hindlimb stimulation in rats during anesthesia with N_2O and O_2 at hyperbaric pressures of 2.25 ATA (atmospheres absolute pressure). Evoked potential amplitude decreases were more sensitive than latency prolongation to the depressant effects of N_2O. The end-tidal N_2O concentrations at which the evoked potentials were recorded were *a*, 0%; *b*, 31% (0.31 ATA); *c*, 68% (0.68 ATA); *d*, 118% (1.18 ATA); *e*, 164% (1.64 ATA). (The *dashed vertical lines* represent the monitor's moveable cursors used to denote the wave points for measurement of amplitude and latency.)

Discussion

For the first time, the MAC of N_2O in rats has been directly measured rather than extrapolated from presumed linear additivity of anesthetics or individual anesthetic lipid solubility. The measured N_2O MAC of 1.55 ± 0.16 ATA is similar to, but exceeds, the value of 1.36 ATA predicted from its lipid solubility and addition to halothane (2) and is less than the 2.20 ATA value assumed if enflurane and N_2O potencies were linearly additive (3). The value is closer to the 1.47 ± 0.076 ATA reported for N_2O MAC by Wardley-Smith and Halsey (6). Although the number of animals tested was not reported, the noxious stimuli were electrical shocks.

The MAC value of an anesthetic can be altered by differences in animal physiology. All animals tested were of similar age and weight. Temperature was maintained and was stable; end-tidal CO_2 was also stable. Although rat brain fatty acid varies with dietary manipulation and can alter volatile anesthetic potency (11), diets were standard and consistent. The

Table 2. Effects of N_2O on Somatosensory Cortical Evoked Potentials in Rats

	Cortical evoked potentials							
	Latency (ms)				Amplitude (μV)			
N_2O (ATA)	P13	P32	N18	N45	P13	P32	N18	N45
0	13	29	18	45	3.28	3.69	2.12	4.51
0.46	13.3	28	18	44	1.93	3.46	0.72	4.10
0.73	13.3	28	18	44	1.59	2.93	0.70	3.46
0.96	14.1	27.3	17.2	47.7	1.11	2.52	0.76	2.40
1.24	28.9	—[a]	46.9	—[a]	1.64	—[a]	2.28	—[a]

ATA, 1 atm absolute pressure.
[a] Waveform was altered, and analysis could not be performed.

time-course of each experiment was similar, and all were performed during daytime working hours. Isoflurane was administered for initial anesthesic induction and instrumentation. This was discontinued immediately before compression and was absent in expired breath for at least 30 min before testing. Although this should not have influenced MAC values found, perhaps residual isoflurane was present in brain and body tissues. Nitrogen was not present in the ventilating gases, so nitrogen narcosis was not an influencing factor.

The noxious stimulus used for MAC determination was electrical stimulation rather than clamping of the proximal tail. Determination of MAC by supramaximal electrical stimulation has been documented to be accurate and reliable in rats (6,9,12,13), dogs (14,15), and humans (16). The electrical stimulation was applied subdermally to the lower abdomen. This location was thought to decrease the likelihood of the needle electrode becoming disconnected from the animal during movement associated with positive responses while still inside the closed hyperbaric chamber; as well, the likelihood of tissue burns was thought to be less. In previous MAC studies, electrical stimulation has been applied to the base of the tail (12), the cheek, and other membrane surfaces (9). Indeed, 10-V electrical stimuli have been reported to be painful and therefore useful for MAC measurement when applied by needle electrodes to the human forearm (9,16). Electrical stimulation has also been reliably used with stimulating electrodes placed subcutaneously in the lower abdomen (as in the present study) and the perineum (14). The electrical stimulation used was of sufficient intensity, and the needle insertion sites were appropriate for reliable repetition of stimuli. Inside an animal hyperbaric chamber, remotely controlled tail-clamp applications were found to be technically unreliable. Remote control of the electrical stimulation functioned consistently.

To test the electrical stimulator, we compared supramaximal electrical stimulation, as used in the present study, with standard tail cross-clamping for isoflurane MAC measurements in Sprague-Dawley rats and found no difference between values found with each type of noxious stimulus. The isoflurane MAC of 1.31% ± 0.08% found in these comparisons was the same as the isoflurane MAC of 1.38% ± 0.02% reported by White et al. (17) when 58 rats were tested by tail-clamp stimulation.

The question of anesthetic tolerance was not addressed. The MAC values were determined between 90 and 120 min after N_2O anesthesia was initiated; therefore, measurements were performed after a consistent N_2O exposure time. Although performed in only two animals, repeat MAC measurements performed 1 h after the initial determinations were not different from the initial MAC value found. Tolerance has been shown to be present in mice, but it is suggested to occur after the first few minutes of anesthesia (18). The EEG changes from N_2O in humans under halothane anesthesia were demonstrated to be less depressed when N_2O was added a second time after being discontinued for 20–30 min (19). If N_2O tolerance had an effect on the measured MAC, it was not discerned, and avoidance of the effects was not possible.

The monitored neuroelectrical effects of N_2O were similar to those previously reported (20–22). Beta (>13 Hz) and alpha (8–13 Hz) brain wave activity both decreased with increasing N_2O partial pressures. There was a preponderance of higher amplitude, slow brain wave activity with N_2O anesthesia. However, increased delta (0–3 Hz) wave activity was not documented, but theta (4–7 Hz) wave activity commonly occurred at >1.0 ATA N_2O. The EEG activity in the theta range was predominant at ≥1.5 ATA N_2O. Both somatosensory and auditory CEP amplitude and latency have been shown to be decreased and increased, respectively, in humans during inhalation of 33% or 40% N_2O (23,24). The effects of N_2O on CEP may be more graded in humans than those demonstrated in rats (25).

The MAC of N_2O in rats is 1.55 ATA when directly measured with electrical stimulation as a noxious stimulus. During anesthesia with N_2O alone in rats, cortical neuroelectrical activity was progressively depressed as the partial pressure increased, although the EEG fast-wave suppression and amplitude increase may not occur at as low a partial pressure as previously demonstrated in humans.

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Hemodynamic and Organ Blood Flow Responses to Halothane and Sevoflurane Anesthesia During Spontaneous Ventilation

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This study compared systemic hemodynamic and organ blood flow responses to equipotent concentrations of halothane and sevoflurane during spontaneous ventilation in the rat. The MAC values for halothane and sevoflurane were determined. Cardiac output and organ blood flows were measured using radiolabeled microspheres. Measurements were obtained in awake rats (control values) and at 1.0 MAC halothane or sevoflurane. The MAC values (mean ± SEM) for halothane and sevoflurane were 1.10% ± 0.05% and 2.40% ± 0.05%, respectively. The $Paco_2$ increased to a similar extent in both groups compared with control values. During halothane anesthesia, heart rate decreased by 12% ($P < 0.01$), cardiac index by 26% ($P < 0.01$), and mean arterial blood pressure by 18% ($P < 0.01$) compared with control values. Stroke volume index and systemic vascular resistance did not change. During sevoflurane anesthesia, hemodynamic variables remained unchanged compared with control values. Coronary blood flow decreased by 21% ($P < 0.01$) and renal blood flow by 18% ($P < 0.01$) at 1.0 MAC halothane, whereas both remained unchanged at 1.0 MAC sevoflurane. Cerebral blood flow increased to a greater extent with halothane (63%; $P < 0.01$) than with sevoflurane (35%; $P < 0.05$). During halothane anesthesia, hepatic arterial blood flow increased by 48% ($P < 0.01$), whereas portal tributary blood flow decreased by 28% ($P < 0.01$). During sevoflurane anesthesia, hepatic arterial blood flow increased by 70% ($P < 0.01$) without a concomitant reduction in portal tributary blood flow. Total liver blood flow decreased only with halothane (16%; $P < 0.05$). In conclusion, for comparable increases in $Paco_2$, systemic hemodynamic and organ blood flow responses to halothane are significantly greater than the responses to sevoflurane at an equipotent concentration of 1.0 MAC in the spontaneously ventilating rat.

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The response of the cardiovascular system to inhaled anesthetics includes alterations in systemic hemodynamics and blood flow to a number of vascular beds. These hemodynamic responses differ when ventilation is spontaneous rather than controlled (1–4), owing, in part, to a higher $Paco_2$ and a lower mean intrathoracic pressure during spontaneous ventilation. The inhaled anesthetic sevoflurane is a halogenated methyl isopropyl ether with hemodynamic properties that have been studied in ventilated animals (5–7). Sevoflurane has a low blood-gas partition coefficient and a nonirritating odor (8,9). These properties augur well for the use of sevoflurane to induce anesthesia in children. It is therefore important to have a clear understanding of the hemodynamic alterations produced when sevoflurane is administered during spontaneous ventilation. Of the inhaled anesthetics currently available, halothane is the most common anesthetic used to induce anesthesia in pediatric patients. Halothane would therefore appear to be a suitable reference anesthetic with which to compare the hemodynamic properties of sevoflurane.

The present study was undertaken to compare systemic hemodynamic and organ blood flow responses to 1.0 MAC halothane with those to an equipotent concentration of sevoflurane during spontaneous ventilation in the rat.

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Methods

After the protocol was approved by our Animal Care Committee, Sprague-Dawley rats (weight 260–320 g) were housed in a temperature- and humidity-controlled environment with a 12-h light/dark cycle. Before the experiments, the rats fasted overnight, with water available ad libitum.

The MAC values for halothane ($n = 8$) and sevoflurane ($n = 8$) were determined in 16 fasted rats using a tail-clamp technique (10,11). Rectal temperature was monitored, and normothermia was maintained using radiant heating lamps.

During ether anesthesia of 15–20-min duration, polyethylene catheters (Tygon; PE 50) were inserted in the left femoral artery for blood pressure monitoring, blood sampling, and reference sample withdrawal, and the left ventricle via the right common carotid artery for injection of radioactive microspheres, as previously described (12). Placement of the catheter in the left ventricle was verified by monitoring the blood pressure waveform. Incisions were infiltrated with 1% lidocaine, and the cannulas were capped with rubber injection ports and tunneled subcutaneously to the midback of the rat, where they were brought to the skin surface. After the operative procedure, the rats were allowed to recover in a temperature-controlled environment for 4 h. There was no obvious evidence of stress or pain during recovery. In previous studies, we showed that indices of stress, such as blood glucagon level, mean arterial pressure, and heart rate, remain unchanged after these operative procedures (12).

After recovery, the rats ($n = 45$) appeared comfortable and resumed their usual behavior. They were placed in cylindrical plexiglass chambers through which oxygen (5 L/min) was administered. After 20 min of stable hemodynamics, heart rate, mean arterial pressure, and arterial blood gases were recorded, and cardiac output and organ blood flows were determined using ^{57}Co-labeled microspheres. The rats were then randomly assigned to receive either 1.0 MAC halothane or sevoflurane. Thirty minutes after the start of anesthetic administration, heart rate, mean arterial pressure, and arterial blood gases were measured, and ^{46}Sc-labeled microspheres were injected to determine cardiac output and organ blood flows. In previous control studies, values for cardiac output and organ blood flows obtained with ^{46}Sc-labeled microspheres were similar to those obtained 30 min earlier with ^{57}Co-labeled microspheres in awake rats (F. J. Carmichael et al., unpublished observations). In the present study, all measurements were performed during periods of stable hemodynamics. Throughout the study period, ventilation was spontaneous, and normothermia was maintained using radiant heating lamps. Inspired anesthetic concentration was monitored continuously using a calibrated infrared medical gas analyzer (SensorMedics LB 2, Anaheim, Calif.). Rectal temperatures taken at the end of the experiments were 37.3° ± 0.3°C (mean ± SEM).

Arterial blood pressure was monitored using a physiograph (Narco Biosystems, Houston, Tex.). Heart rate was determined from the blood pressure waveform. Cardiac output and organ blood flows were measured using 16.5 ± 0.1-μm-diameter radiolabeled microspheres (New England Nuclear, Boston, Mass.). The microspheres, prepared as previously described (13), were suspended in 10% dextran containing 1 drop of Tween-80, agitated for 10 min using a Vortex mixer, and aspirated into polyethylene tubing for gamma-scintillation counting (Nuclear Chicago counter, model 1185, Chicago, Ill.) just before injection. Approximately 40,000–50,000 microspheres were then infused into the left ventricle over 20 s using an infusion pump. A 0.6-mL reference sample that contained 300–400 microspheres was obtained from the femoral artery using a withdrawal pump that began to aspirate blood 10 s before the infusion of microspheres and continued for 60 s. The presence of this number of microspheres in the reference sample has been shown to yield valid cardiac output measurements (14). An equal volume of ficoll (0.6 mL, 13% wt/vol) (Sigma Chemical Co., St. Louis, Mo.), a nonionic synthetic polymer of sucrose, was flushed through the microsphere infusion tubing to replace the volume of blood sampled. The infusion of microspheres and the withdrawal of the reference sample had no demonstrable effect on monitored hemodynamic variables. The net counts infused were the difference between the counts obtained before injection into the left ventricle and those remaining in the polyethylene tubing. At the termination of the study, the rats were killed with intravenous KCl, and the following organs were removed and placed in saline-containing vials for analysis of radioactivity: brain, lungs, heart, liver, kidneys, spleen, stomach, omentum, pancreas, and small and large intestines. All organs were analyzed intact, with the exception of the liver and small intestine, which were each divided into five sections. The mixing of microspheres in the circulation was considered to be adequate if the difference between the right and left renal blood flows was <15% (12). Three rats were eliminated from the study on the basis of this criterion.

Mean arterial pressure was calculated as diastolic pressure plus one-third the pulse pressure. Corrections for overlap during counting of the radioisotopes were made. Cardiac index (Qt) ($\mathrm{mL \cdot min^{-1} \cdot kg\ body\ wt^{-1}}$) was calculated by the equation

Table 1. Systemic Hemodynamics and Arterial Blood Gases in the Spontaneously Ventilating Rat, Awake (Control) and During 1.0 MAC Halothane or Sevoflurane

	Halothane (n = 22)		Sevoflurane (n = 20)	
Physiologic variable	Awake	1.0 MAC	Awake	1.0 MAC
HR (beats/min)	370 ± 8	325 ± 6[a]	360 ± 6	362 ± 10[b]
SVI (mL/kg)	0.63 ± 0.03	0.53 ± 0.04	0.69 ± 0.04	0.65 ± 0.05[c]
Qt ($mL \cdot min^{-1} \cdot kg^{-1}$)	232 ± 7	172 ± 8[a]	250 ± 8	236 ± 8[b]
MAP (mm Hg)	106 ± 3	87 ± 4[a]	105 ± 2	103 ± 4[b]
SVR ($mm\ Hg \cdot mL^{-1} \cdot min \cdot kg$)	0.46 ± 0.01	0.50 ± 0.02	0.42 ± 0.03	0.44 ± 0.02
$Paco_2$ (mm Hg)	37 ± 3	50 ± 2[a]	39 ± 2	48 ± 3[a]
pHa	7.39 ± 0.02	7.33 ± 0.02	7.41 ± 0.01	7.36 ± 0.07
Pao_2 (mm Hg)	385 ± 11	410 ± 14	391 ± 16	414 ± 12

HR, heart rate; SVI, stroke volume index; Qt, cardiac index; MAP, mean arterial pressure; SVR, systemic vascular resistance; pHa, arterial pH.
Values are mean ± SEM.
[a] $P < 0.01$, compared with respective control.
[b] $P < 0.01$, compared with halothane.
[c] $P < 0.05$, compared with halothane.

$$Qt = \frac{Ci \cdot R}{Cr \cdot w},$$

where Ci is net counts injected, R the reference sample withdrawal rate, Cr the net counts in the reference sample, and w the body weight (kg). Organ blood flow (Qo) ($mL \cdot min^{-1} \cdot kg$ body wt^{-1}) was calculated by the equation

$$Qo = \frac{Qt \cdot Co}{Ci},$$

where Co is net counts in the organ. Systemic vascular resistance ($mm\ Hg \cdot mL^{-1} \cdot min \cdot kg$) was calculated as the quotient of the mean arterial pressure and cardiac index. Central venous pressure was assumed to approximate zero. Stroke volume index (mL/kg) was calculated as the quotient of cardiac index and heart rate. Organ vascular resistances ($mm\ Hg \cdot mL^{-1} \cdot min \cdot kg$) were calculated as the quotient of the mean arterial pressure and organ blood flow.

Portal tributary blood flow (PTBF) was calculated as the sum of the blood flow to the spleen, stomach, omentum, pancreas, and small and large intestines. The contribution of blood flows from the pancreas and omentum, which cannot be readily isolated in the rat, is included in the flows to the small and large intestines. The accuracy of this method as an estimate of PTBF is well validated (15,16). Hepatic arterial blood flow (HABF) was determined from the net counts within the liver. Total hepatic blood flow was calculated as the sum of the PTBF and HABF.

Cardiac output, stroke volume, organ blood flows, and vascular resistances were indexed to body weight (kg). Because the relationship of organ weight to body weight did not change throughout the study period, there are no differences in the conclusions derived when this form of expression is used as opposed to blood flows expressed per gram organ.

Data are presented as mean ± SEM. Statistical significance ($P < 0.05$) was determined using one-way analysis of variance. Intergroup differences were determined by the least-significant difference method (17).

Results

The MAC values (mean ± SEM) for halothane and sevoflurane were 1.10% ± 0.05% and 2.40% ± 0.05%, respectively. The $Paco_2$ increased from a control value of 37 ± 3 to 50 ± 2 mm Hg with halothane ($P < 0.01$) and from 39 ± 4 to 48 ± 3 mm Hg with sevoflurane ($P < 0.01$) (Table 1). The differences in $Paco_2$ at 1.0 MAC were not significant. The pHa and Pao_2 did not differ between groups either as control values or at 1.0 MAC (Table 1).

Control (awake) hemodynamic measurements were similar in the two groups (Table 1). Compared with control measurements, heart rate decreased by 12% ($P < 0.01$), cardiac index by 26% ($P < 0.01$), and mean arterial pressure by 18% ($P < 0.01$) during halothane anesthesia (Figure 1). These variables remained unchanged during sevoflurane anesthesia compared with control values (Figure 1). Stroke volume index and systemic vascular resistance did not change during administration of either anesthetic (Table 1).

Control organ blood flow measurements were similar in the two groups (Table 2). Compared with control measurements, coronary blood flow decreased by 21% ($P < 0.01$) (Figure 2) without a significant change in coronary vascular resistance (Table 3) during halothane anesthesia. In contrast, neither coronary blood flow (Figure 2) nor coronary vascular resistance (Table 3) changed during sevoflurane administration. Cerebral blood flow increased

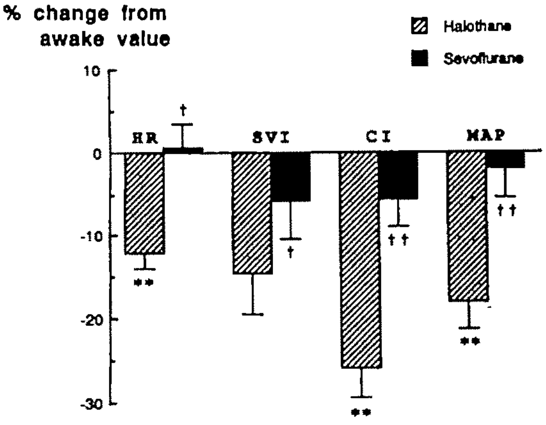

Figure 1. Systemic hemodynamic responses to 1.0 MAC halothane or sevoflurane anesthesia in the spontaneously ventilating rat. Data are presented as percent change from the control (awake) values shown in Table 1. HR, heart rate; SVI, stroke volume index; CI, cardiac index; MAP, mean arterial pressure. $^{**}P < 0.01$, compared with control (awake) value. $^{\dagger}P < 0.05$, compared with halothane. $^{\dagger\dagger}P < 0.01$, compared with halothane.

by 63% ($P < 0.01$) (Figure 2), whereas cerebral vascular resistance decreased by 50% ($P < 0.01$) (Table 3) during halothane anesthesia. During sevoflurane anesthesia, the changes in cerebral blood flow and vascular resistance were less marked, 35% ($P < 0.05$) (Figure 2) and 27% ($P < 0.05$) (Table 3), respectively. Renal blood flow decreased by 18% ($P < 0.01$) (Figure 2) without a change in renal vascular resistance during halothane anesthesia. Neither renal blood flow (Figure 2) nor renal vascular resistance (Table 3) changed during sevoflurane administration. Blood flow to the lungs was similar in awake and anesthetized rats, suggesting that arteriovenous shunting of microspheres did not occur during anesthesia.

The HABF increased by 48% ($P < 0.01$) (Figure 3) in association with a 44% ($P < 0.01$) decrease in hepatic arterial vascular resistance during halothane anesthesia (Table 3). Similarly, HABF increased by 70% ($P < 0.01$) (Figure 3), and hepatic arterial vascular resistance decreased by 42% ($P < 0.01$) during sevoflurane anesthesia (Table 3). The increase in HABF was associated with a reduction in PTBF during halothane (28%; $P < 0.01$) but not during sevoflurane anesthesia. Portal tributary vascular resistance did not change during administration of either halothane or sevoflurane (Table 3). Total hepatic blood flow decreased only with halothane (16%; $P < 0.05$) (Figure 3).

Splenic blood flow decreased by 38% ($P < 0.01$) during halothane anesthesia and by 24% ($P < 0.05$) during sevoflurane anesthesia (Table 2), with corresponding increases in splenic vascular resistance of 38% ($P < 0.05$) and 28% (NS), respectively (Table 3). Gastric blood flow decreased by 32% ($P < 0.01$) after halothane and by 29% ($P < 0.01$) after sevoflurane (Table 2), with corresponding increases in gastric vascular resistance of 21% (NS) and 42% ($P < 0.05$), respectively (Table 3). Small and large intestinal blood flows decreased by 27% ($P < 0.01$) and 14% ($P < 0.01$), respectively, after halothane (Table 2), with no change in vascular resistances (Table 3).

Discussion

The present study compared systemic hemodynamic and organ blood flow responses to 1.0 MAC halothane with those to an equipotent concentration of sevoflurane in the spontaneously ventilating rat. It is important to study the hemodynamic effects of inhaled anesthetics during spontaneous ventilation, because this anesthetic technique is commonly used in both pediatric and adult anesthesia, particularly for

Table 2. Organ Blood Flow Responses in the Spontaneously Ventilating Rat, Awake (Control) and During 1.0 MAC Halothane or Sevoflurane

Organ blood flow ($mL \cdot min^{-1} \cdot kg^{-1}$)	Halothane ($n = 22$)		Sevoflurane ($n = 20$)	
	Awake	1.0 MAC	Awake	1.0 MAC
Coronary	8.2 ± 0.4	6.5 ± 0.4^{a}	9.0 ± 0.6	8.9 ± 0.4^{b}
Cerebral	3.8 ± 0.2	6.2 ± 0.7^{a}	4.3 ± 0.3	$5.8 \pm 0.6^{c,d}$
Renal	38.9 ± 1.6	31.9 ± 1.9^{a}	44.0 ± 1.5	44.9 ± 2.1^{b}
Splenic	4.6 ± 0.3	2.8 ± 0.3^{a}	5.1 ± 0.3	$3.9 \pm 0.4^{c,d}$
Gastric	3.1 ± 0.2	2.1 ± 0.2^{a}	3.4 ± 0.2	2.4 ± 0.2^{a}
Small intestine	21.6 ± 1.3	15.7 ± 0.9^{a}	24.8 ± 1.4	25.1 ± 1.5^{b}
Large intestine	8.9 ± 0.6	6.8 ± 0.6^{c}	8.9 ± 0.6	7.8 ± 0.6
Hepatic arterial	8.6 ± 0.7	12.7 ± 1.1^{a}	8.7 ± 0.7	14.8 ± 1.1^{a}
Portal tributary	38.2 ± 1.5	27.4 ± 1.3^{a}	42.4 ± 1.8	39.0 ± 1.9^{b}
Total hepatic	46.8 ± 1.5	40.1 ± 1.8^{c}	51.1 ± 1.6	53.8 ± 2.2^{b}

Values are mean ± SEM.
$^{a}P < 0.01$, compared with respective control.
$^{b}P < 0.01$, compared with halothane.
$^{c}P < 0.05$, compared with respective control.
$^{d}P < 0.05$, compared with halothane.

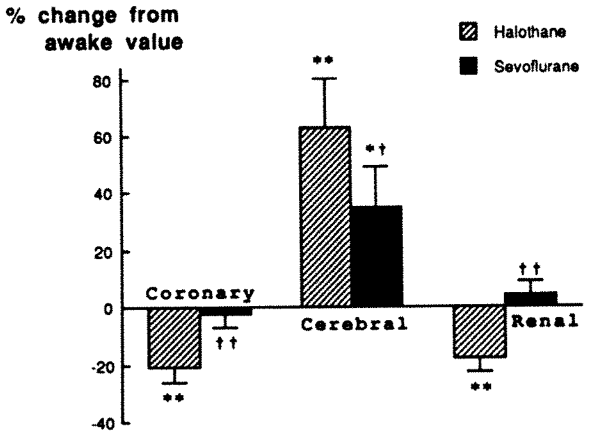

Figure 2. Coronary, cerebral, and renal blood flows during 1.0 MAC halothane or sevoflurane anesthesia in the spontaneously ventilating rat. Data are presented as percent change from the control (awake) values shown in Table 2. $^*P < 0.05$, compared with control (awake) value. $^{**}P < 0.01$, compared with control (awake) value. $†P < 0.05$, compared with halothane. $††P < 0.01$, compared with halothane.

outpatients. Hemodynamic alterations that occur during inhaled anesthesia may be attributed not only to direct pharmacologic effects of the anesthetic, but also to an increase in Pa_{CO_2}. Other factors, including alterations in autonomic outflow, cardiac output, mean arterial pressure, and oxygen requirements, may alter organ blood flow. To help ensure that the conditions of the present study were parallel to those of clinical inhaled anesthesia, no attempt was made to regulate these factors. In agreement with a previous study (18), the increase in Pa_{CO_2} observed in the present study with 1.0 MAC halothane was similar to that with 1.0 MAC sevoflurane. An increase in Pa_{CO_2} of this magnitude might have attenuated the hemodynamic depression induced by the inhaled anesthetics (1,3,19). Nevertheless, the present data demonstrate that for comparable increases in Pa_{CO_2} during spontaneous ventilation, sevoflurane produces minimal hemodynamic alterations compared with halothane.

Inspired rather than end-tidal anesthetic concentrations were measured in the present study. An estimation of anesthetic requirement based on inspired anesthetic concentration assumes the equilibration of inspired, alveolar, and brain anesthetic tensions. The time to attain equilibrium is influenced by the solubility of the anesthetic and its effect on minute ventilation (10). In the present study, the effect of sevoflurane on minute ventilation was similar to that of halothane, which negates a differential effect of this variable on equilibration. However, the solubilities of the two anesthetics differ (8,9). For an anesthetic with a blood-gas partition coefficient similar to that of sevoflurane, the ratio of end-tidal to inspired anesthetic concentration has been shown to approach unity within 30 min in the rat (20). In the present study, therefore, it is likely that the inspired concentration of sevoflurane closely reflected the alveolar or end-tidal value when hemodynamic and organ blood flow values were determined. It is probable that the greater solubility of halothane may have delayed equilibration beyond 30 min. However, previous studies in rats report that the end-tidal to inspired ratio of halothane was within 10% of unity after 25–35 min (10). In addition, the use of end-tidal measurements of halothane concentration yielded a MAC value for halothane in the rat similar to that found in the present study (10). Furthermore, had a longer time been allowed for equilibration in the present study, it is probable that even greater differential effects on systemic hemodynamics and organ blood flows would have been observed.

Awake values are in agreement with those of previous dose-response studies from this laboratory on the hemodynamic effects of MAC multiples of

Table 3. Vascular Resistances in the Spontaneously Ventilating Rat, Awake (Control) and During 1.0 MAC Halothane or Sevoflurane

Vascular resistance ($mm\ Hg \cdot mL^{-1} \cdot min \cdot kg$)	Control ($n = 22$)	Halothane ($n = 22$)	Control ($n = 20$)	Sevoflurane ($n = 20$)
Coronary	12.9 ± 0.8	13.4 ± 1.5	11.7 ± 0.9	11.6 ± 0.8
Cerebral	27.9 ± 2.2	14.0 ± 1.6^a	24.4 ± 2.5	17.8 ± 0.6^b
Renal	2.7 ± 0.1	2.7 ± 0.2	2.4 ± 0.1	2.3 ± 0.1
Splenic	22.6 ± 2.7	31.1 ± 3.2^c	20.6 ± 2.7	26.4 ± 3.3
Gastric	34.2 ± 2.4	41.4 ± 5.2	30.1 ± 2.4	42.9 ± 4.2^c
Small intestine	4.9 ± 0.4	5.5 ± 0.4	4.2 ± 0.3	4.1 ± 0.3^b
Large intestine	11.9 ± 1.1	12.8 ± 3.7	11.8 ± 1.1	13.2 ± 1.4
Hepatic arterial	12.3 ± 1.1	6.9 ± 1.8^a	12.1 ± 1.1	7.0 ± 0.7^a
Portal tributary	2.8 ± 0.1	2.2 ± 0.2	2.5 ± 0.1	2.5 ± 0.1

Values are mean ± SEM.
$^aP < 0.01$, compared with respective control.
$^bP < 0.05$, compared with halothane.
$^cP < 0.05$, compared with respective control.

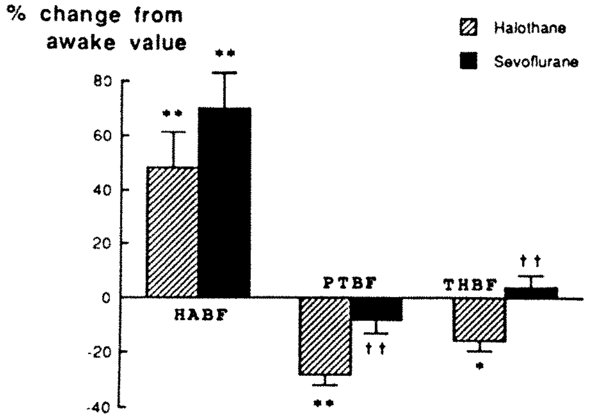

Figure 3. Hepatic arterial (HABF), portal tributary (PTBF), and total hepatic (THBF) blood flows during 1.0 MAC halothane or sevoflurane anesthesia in the spontaneously ventilating rat. Data are presented as percent change from the control (awake) values shown in Table 2. $^{*}P < 0.05$, compared with control (awake) value. $^{**}P < 0.01$, compared with control (awake) value. $^{††}P < 0.01$, compared with halothane.

sevoflurane (11) and halothane (21). For comparable increases in Pa_{CO_2} in the present study, systemic hemodynamics were affected to a greater extent by halothane than by an equipotent concentration of sevoflurane. Consistent with these findings, sevoflurane decreased hemodynamic variables to only a small extent in newborn swine (22). Greater reductions in stroke volume, cardiac output, and mean arterial pressure were reported to occur during sevoflurane anesthesia in mature swine (5) and in rats (7). The difference between the results of the present study and those in mature swine (5) may be attributed in part either to the hyperdynamic state of the spontaneously breathing awake swine or to the introduction of controlled ventilation during sevoflurane anesthesia. The discrepancy in the study in rats (7) may also be due to an effect of controlled ventilation or, more likely, to the simultaneous presence of two other anesthetics, chloral hydrate and chloralose, in that study.

The microsphere technique yields an accurate estimate of organ blood flows, provided that several important criteria are satisfied (12,13,23). The validity of the awake blood flow measurements in the present study is substantiated by previous work from this laboratory (11,12) and from a number of other investigators (13,14,24).

The response of the coronary circulation to halothane in the present study is consistent with the reports of other investigators (25). The lack of an effect of sevoflurane on coronary blood flow is of interest, because both a decrease (5) and an increase (6) in coronary blood flow have been reported during sevoflurane anesthesia. The decrease in coronary blood flow may be attributed to the administration of a general anesthetic in swine with elevated hemodynamic variables in the awake state, whereas the increase in coronary blood flow observed in dogs was associated with a 60% increase in heart rate and thus might have reflected an increase in myocardial oxygen requirement.

For comparable increases in Pa_{CO_2}, cerebral blood flow increased, and cerebral vascular resistance decreased to a greater extent during halothane than during sevoflurane anesthesia. This finding suggests that the cerebrovascular effects of halothane exceed those of sevoflurane. In support of this observation, the effects of sevoflurane on cerebral blood flow, cerebral oxygen requirement, and intracranial pressure were recently shown to compare favorably with those of isoflurane (26).

During hypercarbia, HABF has been reported to either remain unchanged (27) or to decrease transiently, followed by a return to control values (28). It is unlikely therefore that the increase in HABF observed in the present study with both halothane and sevoflurane is due to an effect of hypercarbia. Indeed, this increase in flow is consistent with the reports of other investigators (5,11,21,29–31) and may represent either a reciprocal change associated with reduced PTBF, in the case of halothane (21), or, a direct pharmacologic action of the inhaled anesthetics on hepatic arterial vasculature.

In the present study, the changes in PTBF were not associated with alterations in portal tributary vascular resistance but, rather, paralleled the changes in cardiac output. Although hypercarbia has been associated with portal tributary vasodilation and an increase in flow (27,28), PTBF did not increase under the conditions of the present study. In fact, PTBF decreased with halothane. These observations are consistent with previous reports that inhaled anesthetics may attenuate the response of the portal circulation to hypercarbia (32) and suggest that PTBF depends to a greater extent on changes in cardiac output than on changes in Pa_{CO_2} in the presence of potent anesthetics.

In summary, systemic hemodynamics and organ blood flows are disturbed to a greater extent by 1.0 MAC halothane than by an equipotent concentration of sevoflurane during spontaneous ventilation. These results have clinical implications and suggest that sevoflurane may be advantageous when hemodynamic stability is required during an inhaled induction of anesthesia.

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Halothane Enhances Pulmonary Artery Endothelial Eicosanoid Release

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To determine whether anesthetics alter endothelial eicosanoid release, cultured bovine pulmonary artery endothelial cells were studied during constant flow and pressure perfusion at two oxygen tensions (hypoxia, 50 ± 2 mm Hg; normoxia, 144 ± 5 mm Hg; mean ± SEM) with and without 1% halothane. Endothelialized microcarriers containing ~5 × 10^6 cells were loaded into cartridges and perfused (3 mL/min) with Krebs' solution (pH 7.4, at 37°C) equilibrated with each gas mixture. Eicosanoids (6-keto prostaglandin $F_{1\alpha}$, thromboxane B_2, and total peptidoleukotrienes [C_4, D_4, E_4, F_4]) were measured by radioimmunoassay and quantified per gram of cellular protein per minute. Eicosanoid release did not vary over time. The 6-keto prostaglandin $F_{1\alpha}$ release increased during hypoxia (normoxia 291 ± 27 vs hypoxia 395 ± 35 $ng \cdot min^{-1} \cdot g$ $protein^{-1}$; $P < 0.01$). Halothane (H) increased release of each eicosanoid during both normoxia and hypoxia: 6-keto prostaglandin $F_{1\alpha}$—normoxia 291 ± 27 versus normoxia + H 356 ± 32 $ng \cdot min^{-1} \cdot g$ $protein^{-1}$, hypoxia 395 ± 35 versus hypoxia + H 464 ± 40 $ng \cdot min^{-1} \cdot g$ $protein^{-1}$, $P < 0.05$; thromboxane B_2—normoxia 19 ± 2 versus normoxia + H 26 ± 2 $ng \cdot min^{-1} \cdot g$ $protein^{-1}$, hypoxia 20 ± 2 versus hypoxia + H 38 ± 5 $ng \cdot min^{-1} \cdot g$ $protein^{-1}$, $P < 0.001$; leukotriene—normoxia 363 ± 35 versus normoxia + H 489 ± 52 $ng \cdot min^{-1} \cdot g$ $protein^{-1}$, hypoxia 329 ± 29 versus hypoxia + H 455 ± 39 $ng \cdot min^{-1} \cdot g$ $protein^{-1}$, $P = 0.001$. We conclude that alteration of endothelial eicosanoid release by halothane and hypoxia could modulate pulmonary vascular tone.

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Anesthetics alter vascular tone and inhibit hypoxic pulmonary vasoconstriction (HPV) (1,2). This has been attributed to many factors, including alterations in autonomic activity and direct anesthetic effects on vascular smooth muscle. Because the endothelium is intimately involved in the regulation of both systemic and pulmonary vascular resistance (PVR), a further explanation for the effect of anesthetics could be either the potentiation or inhibition of the release of endothelial-derived vasodilators, such as prostacyclin or nitric oxide, or both, or endothelial-derived vasoconstrictors, such as thromboxane, leukotrienes, or endothelin, or all of these (3–5). Modulation of endothelial function by inhaled anesthetics could, in part, mediate their vascular effects (1,2,6–10). Although the anesthetic modulation of endothelial-derived relaxing factor has recently been studied (10), the effect of anesthetics on endothelial eicosanoid release has received little attention. A relationship between endothelial eicosanoid release and inhaled anesthetics-mediated vasodilation was suggested by Stone and Johns (10), but whether volatile anesthetics directly affect endothelial eicosanoid release is not known.

Pulmonary vascular resistance and its relation to oxygen tension is influenced by many factors, including volatile and intravenous anesthetics (1,2,11,12). Despite numerous investigations to define how anesthetics and oxygen interact to influence PVR, unanswered questions remain. Pulmonary artery endothelium produces numerous eicosanoids, some potent vasoconstrictors (thromboxane, prostaglandin $F_{2\alpha}$ [$PGF_{2\alpha}$]), and other potent vasodilators (prostacyclin, prostaglandin E_1 [PGE_1]) (13,14). Studies in intact animals and isolated lungs have demonstrated eicosanoid involvement in the pulmonary vascular response to hypoxia (11). In vitro studies in static endothelial cells have failed to clearly demonstrate altered eicosanoid release by hypoxia (15–17). These studies, however, did not include the important physiologic factor, shear stress, which is ever present in perfused, in vivo endothelium (18,19).

This study was designed to determine whether halothane alters the release of prostacyclin, thromboxane, and total peptidoleukotriene (C_4, D_4, E_4, F_4)

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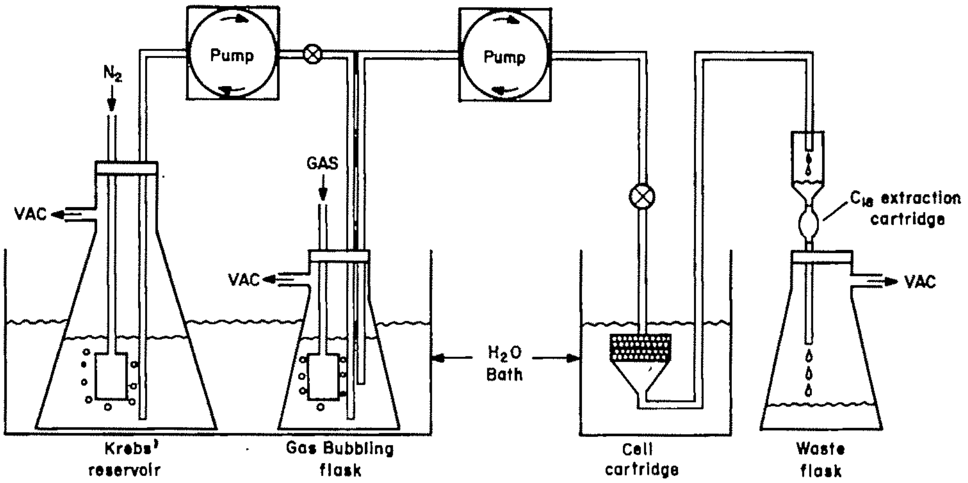

Figure 1. The perfusion circuit. Krebs' solution bubbled with 100% N_2 was pumped via a multichannel variable-speed roller-head pump to the gas-bubbling flask. Krebs' perfusate oxygen tension and halothane concentration was controlled by bubbling gas (1 L/min) of known oxygen tension (normoxia, 21% O_2; hypoxia, 4% O_2; normoxia + 1% halothane; hypoxia + 1% halothane) through the perfusate. The perfusate was pumped through the cell cartridge containing 5 × 10^6 pulmonary artery endothelial cells on microcarrier beads to the C_{18} Sep-Pak extraction cartridge and into a vacuum (VAC)-evacuated waste flask. Temperature was maintained at 37°C by immersion of the perfusion circuit components in a servoregulated water bath.

by perfused bovine pulmonary artery endothelial cells during normoxia and hypoxia.

Methods

Cell Culture

Bovine pulmonary artery endothelial cells (CCL-209 CPAE; American Type Culture Collection, Rockville, Md.) >95% pure, as determined by morphology, the presence of factor VIII antigen, angiotensin-converting enzyme activity, and diacyl low-density lipoprotein uptake, were cultured according to the method of Ryan et al. (20). Endothelial cells were suspended in M-199 containing 20% fetal bovine serum, penicillin (50 U/mL), streptomycin (50 μg/mL), and amphotericin (0.25 μg/mL) and initially seeded in 75-cm^2 flasks (Fisher, Orangeburg, N.Y.). Culture flasks were incubated at 37°C in 95% air–5% CO_2 and the medium changed at 24 h and then every 3 days until confluence was reached (5–8 days). The cells were scraped from the flask with a sterile rubber policeman, resuspended, and seeded onto 2 × 10^5 microcarrier beads (Cytodex-3, Sigma Chemical Co., St. Louis, Mo.) hydrated in Dulbecco's phosphate-buffered saline (PBS) and placed in a 100-mL siliconized roller bottle (Gibco, Grand Island, N.Y.). The roller bottle was gassed with 95% air–5% CO_2, sealed, and rotated at 2 rpm for 2 min every 30 min for 3 h and then continuously rotated at 1.5 rpm at 37°C. When cells were confluent on the microcarrier beads, as seen on phase-contrast microscopy, additional microcarrier beads (1 × 10^5) were added to the roller bottle (every 2–3 days) until 5 × 10^5 confluent microcarrier beads were obtained (approximately 3–4 wk). The medium was changed approximately every 2 days and roller bottles were gassed with 95% air–5% CO_2. Twenty-four hours before the experiment, the cell medium in the roller bottles was changed to standard medium enriched with 20 μM arachidonic acid to ensure adequate substrate for eicosanoid release. This supplementation with arachidonate does not alter either prostacyclin release or the proportions of eicosanoids released (15,21,22).

Perfusion System

The perfusion system was designed to perfuse four identical circuits simultaneously with the same pressure and flow characteristics (Figure 1). Each circuit contained a similar number of cells from a single roller bottle. For each experiment (n = 8), cells from a single population were exposed to four conditions (normoxia, normoxia + halothane, hypoxia, hypoxia + halothane) while being identically perfused. Perfusate oxygen tension was controlled by bubbling gas (1 L/min) of known oxygen concentration (normoxia—21% O_2, 5% CO_2, 74% N_2; hypoxia—4% O_2, 5% CO_2, 91% N_2) through the perfusate in a closed, 250-mL vacuum-evacuated Erlenmeyer flask until equilibration occurred (<5 min). Perfusate Po_2, Pco_2, and pH were analyzed (Radiometer ABL 30) in each circuit. Halothane 1% was added to one hypoxic and one normoxic gas mixture by diverting 1 L/min of the respective gases through a calibrated halothane vaporizer (Fraser-Harlake, Orchard Park, N.Y.). Halothane concentration was monitored by a calibrated Servo Gas Monitor 120 (Siemens, Schaumburg, Ill.) before, during, and after each experiment and was constant at 1%.

The perfusion rate (3 mL/min) of the cells was controlled in each circuit by using a single, multichannel, variable-speed, roller-head pump (Masterflex 7553-60; Cole-Parmer Instrument Co., Chicago, Ill.). Perfusate was pumped from the reservoir through the gassing flask to the cell cartridges (25-mm air monitoring cassette; Gelman Sciences, Ann Arbor, Mich.) and then onto a vacuum-extracted C_{18} Sep-Pak cartridge. At this perfusion rate, <4 min was required for oxygen tension in the cell cartridge perfusate to equilibrate with the gassing flask perfusate. Pressure measurements at locations proximal and distal to the cell cartridge showed that perfusate pressure increased linearly with increasing flow and was not measurably different across the cell cartridge. Perfusate pulsatile pressure at the experimental flow rate (3 mL/min) was 9/6 mm Hg (mean 7 mm Hg). The temperature of the perfusate was maintained at 37°C by immersing the reservoir, bubble chamber, and cell cartridges in servoregulated water baths (220 A; Fisher). Filter paper (0.8 μm; Gelman Sciences) was placed in the distal end of the cell cartridge to prevent loss of microcarrier beads and cells. Inspection under a phase-contrast microscope revealed no beads or cells. After perfusion, microcarriers inspected by phase-contrast microscopy demonstrated adherent cells that remained confluent and unchanged in physical appearance.

Experimental Protocol

For each experiment, four circuits were primed with Krebs' solution. The medium was aspirated from the roller bottle, and the microcarrier beads were washed three times with PBS (pH 7.4) and resuspended in 10 mL of Krebs' solution. Two-milliliter samples of this microcarrier bead suspension ($\sim 5 \times 10^6$ cells) were placed into each cell cartridge. A fifth sample was used as a nonperfusion control for protein quantitation. Ten minutes after initiating perfusion, nine successive 20-min aliquots of perfusate lipids were extracted with C_{18} Sep-Pak extraction cartridges (Waters Associates, Milford, Mass.) over the next 3 h.

The lipid portion of the filtrate was eluted from the C_{18} cartridges with methanol. The methanol was vacuum evaporated (Speed Vac Concentrator; Savant, Farmingdale, N.Y.) at 1700 rpm at 4°C and the sample stored at −20°C until assay. During each experiment, perfusate was collected from each circuit just proximal to the cell cartridge for oxygen, carbon dioxide, and pH measurement, as previously described.

Protein Assay

At the end of each experiment, each cell cartridge was washed with distilled water to remove the microcarrier beads and cells. The microcarriers were vortexed, and the quantity of cellular protein from the lysed cells was determined by the method of Bradford (23) (Bio-Rad, Protein Assay; Bio-Rad Laboratories, Richmond, Calif.) using bovine serum albumin as the standard.

Radioimmunoassay of Eicosanoid Release

The assays of 6-keto $PGF_{1\alpha}$, the stable metabolite of prostacyclin; thromboxane B_2 (TXB_2), the stable metabolite of thromboxane A_2 (TXA_2); and total peptidoleukotriene (LT) (C_4, D_4, E_4, F_4) were performed by standard radioimmunoassay techniques, as previously described (24). All assays were performed in duplicate and at room temperature, unless otherwise indicated. The dried lipid extracts were resuspended in 3 mL of 0.1% gelatin (PBS) with 0.02% sodium azide and 50 μL of antiserum (Advanced Magnetics, Cambridge, Mass.), 50 μL of tritiated eicosanoid (6-keto $PGF_{1\alpha}$, TXB_2, LT) (New England Nuclear, Boston, Mass.), and 100-μL samples in duplicate or 100 μL of standards (Advanced Magnetics) in triplicate were incubated in plastic test tubes (2 h for 6-keto $PGF_{1\alpha}$ and TXB_2; 2.5 h for LT at 4°C).

After incubation, 50 μL of 0.5% gelatin PBS was added to each assay tube for 10 min, followed by the addition of 1 mL of dextran-coated charcoal. After incubation in dextran-coated charcoal (10 min for $PGF_{1\alpha}$; 11 min for TXB_2; 15 min for LT), the samples were centerfuged at 2000 rpm for 15 min, and the supernatant, containing antibody-bound radiolabel, was decanted directly into scintillation vials (Beckman, Fullerton, Calif.) with 8 mL of scintillation cocktail added for liquid scintillation counting (Liquid Scintillation Counter; LKB Wallace, Washington, D.C.). The standard curve obtained was logit transformed, and sample potency estimates were calculated by least-square regression of the log dose logit transformation. Antisera used for 6-keto $PGF_{1\alpha}$ and TXB_2 had a cross-reactivity of <0.1% for all other antisera tested. Antisera used for LT had a reactivity for LTC_4 (55%), LTD_4 (100%), LTE_4 (57%), and LTF_4 (67%), and a cross-reactivity for LTB_4 (0.25%), 5-HETE (0.19%), and <0.01% for other prostaglandin products. In other experiments, recovery rates for known amounts of eicosanoid were >90%. The concentrations of 6-keto $PGF_{1\alpha}$ and LT were 10–100 times greater than the lower limit of detection (1.95 pg/0.1 mL) in >95% of the assays. For TXB_2, levels <1.95 pg/0.1 mL were counted as zero.

Table 1. Mean Oxygen, Carbon Dioxide, Hydrogen Ion, and Protein Concentrations of Each Circuit

	Po_2 (mm Hg)	Pco_2 (mm Hg)	pH (U)	Cellular protein (mg)
Normoxia	144 ± 5	30 ± 2	7.30 ± 0.03	0.25 ± 0.05
Normoxia + halothane	143 ± 5	30 ± 2	7.30 ± 0.03	0.26 ± 0.05
Hypoxia	50 ± 2*	28 ± 2	7.34 ± 0.03	0.27 ± 0.08
Hypoxia + halothane	51 ± 3*	28 ± 2	7.32 ± 0.03	0.21 ± 0.04

Mean ± SEM, $n = 8$.
$^*P < 0.001$ versus normoxia.

Statistics

Data are presented as mean ± SEM. Analysis of variance comparing eicosanoid release rates at different oxygen tensions, with and without halothane, over time was performed by a standard computerized statistical program (Crunch Software Corp., Oakland, Calif.). A significant difference among means was determined by the Newman-Keuls method (25). Paired t-tests were used to compare normoxic and hypoxic perfusate system data, with and without halothane. A P value <0.05 was considered significant.

Results

The oxygen tension of the perfusate was significantly lower during hypoxia compared with normoxia (Table 1). There were no differences in perfusate carbon dioxide tension or pH. The quantity of cellular protein recovered was similar from the normoxic and hypoxic circuits (Table 1) and did not differ from the nonperfusion (control) samples.

Because timed aliquots were collected, eicosanoid release (total eicosanoid eluted or released from the cell cartridges) could be quantitated per minute. The amount of eicosanoid released was indexed to the amount of cellular protein measured from each cell cartridge. Therefore, all eicosanoid release rates are expressed in nanograms per minutes per gram of cellular protein ($ng \cdot min^{-1} \cdot g\ protein^{-1}$). The means of the measured concentration of each eicosanoid determined were significantly greater than the lower limit of detection of the assay.

Release of 6-keto $PGF_{1\alpha}$, TXB_2, and LT did not vary over time during each of the four conditions tested. For example, 6-keto $PGF_{1\alpha}$ release over time is demonstrated in Figures 2 and 3. Because the mean release rates of the three different eicosanoids did not vary over time during all conditions tested, the release rates for each condition were combined and are summarized in Table 2. Hypoxia resulted in a significant increase in mean 6-keto $PGF_{1\alpha}$ release. Hypoxia did not alter TXB_2 ($P = 0.5$) or total LT ($P = 0.25$) release. Halothane caused a significant increase in

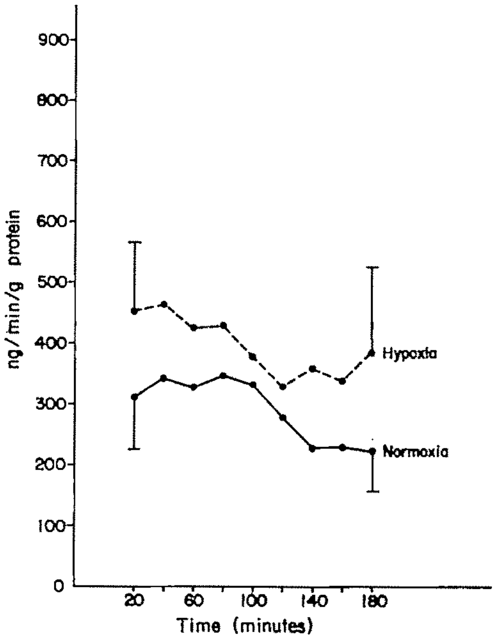

Figure 2. Mean 6-keto $PGF_{1\alpha}$ release ($ng \cdot min^{-1} \cdot g\ protein^{-1}$) over time during normoxia and hypoxia; $n = 8$, mean ± SEM. The 6-keto $PGF_{1\alpha}$ release did not significantly vary over time and was greater during hypoxia ($P \leq 0.01$).

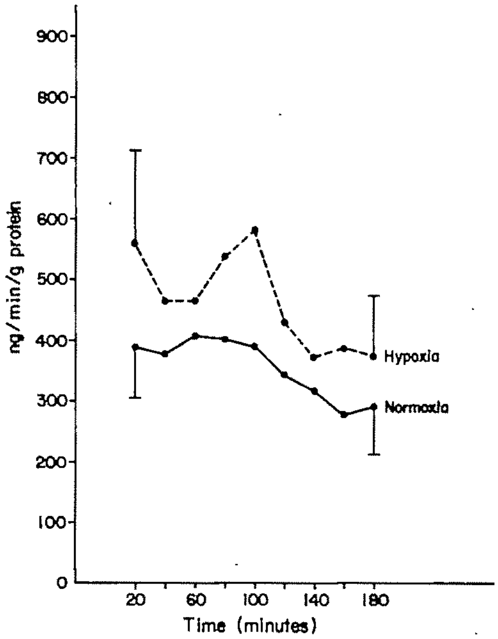

Figure 3. Mean 6-keto $PGF_{1\alpha}$ release ($ng \cdot min^{-1} \cdot g\ protein^{-1}$) over time during normoxia and hypoxia with halothane; $n = 8$, mean ± SEM. The 6-keto $PGF_{1\alpha}$ release did not vary over time and was greater during hypoxia.

Table 2. Mean 6-keto $PGF_{1\alpha}$, Thromboxane B_2 (TXB_2) and Leukotriene (LT) Release

	$PGF_{1\alpha}$ ($ng \cdot min^{-1} \cdot g$ $protein^{-1}$)	TXB_2 ($ng \cdot min^{-1} \cdot g$ $protein^{-1}$)	LT ($ng \cdot min^{-1} \cdot g$ $protein^{-1}$)
Normoxia	291 ± 27	19 ± 2	363 ± 35
Normoxia + halothane	356 ± 32[a]	26 ± 2[a]	489 ± 52[a]
Hypoxia	395 ± 35[b]	20 ± 2	329 ± 29
Hypoxia + halothane	464 ± 40[c,d]	38 ± 5[a,e]	435 ± 39[a]

6-keto $PGF_{1\alpha}$, the stable metabolite of prostacyclin; TXB_2, thromboxane B_2; LT, leukotriene.
Mean ± SEM; $n = 72$.
[a] $P < 0.001$ versus without halothane.
[b] $P < 0.001$ versus normoxia.
[c] $P = 0.015$ versus without halothane.
[d] $P = 0.006$ versus normoxia with halothane.
[e] $P = 0.015$ versus normoxia with halothane.

mean 6-keto $PGF_{1\alpha}$, TXB_2, and LT release during both normoxia and hypoxia.

Discussion

Eicosanoid metabolites play a critical role in the regulation of vascular resistance, particularly in the pulmonary circulation (3–5,13,14). Numerous studies in a wide variety of experimental preparations have demonstrated the role of eicosanoids but have not directly demonstrated whether the endothelium plays a central role. These preparations, which include intact anesthetized animals, isolated perfused lungs, pulmonary vascular strips, and vessel loops, did not directly provide information concerning endothelial function. For example, hypoxia changes pulmonary vascular pressure and flow, and these changes could be responsible for secondary alterations in endothelial eicosanoid release (26–28). On the other hand, in static endothelial cell systems, important physiologic stimuli, flow, and pulsatile pressure are absent.

Perfusion-associated pressure and shear stress critically affect endothelial cell function, including cyclooxygenase activity (29,30). The use of endothelialized microcarriers, in addition to providing a large surface area, permitted the ubiquitous in vivo physiologic environmental factor, flow, to be incorporated into an isolated cell system (26–28). Indeed, in this preparation, flow is the primary stimulus to eicosanoid release (net eicosanoid eluted from the cell cartridges), which is then modulated by halothane and oxygen tension. Thus, it was possible to determine the effects of acute hypoxia and halothane on endothelium exposed to constant flow and pulsatile pressure, analogous to the in vivo situation but without the variability inherent in intact preparations. Therefore the response of perfused endothelium (eicosanoid release) during normoxia and hypoxia, with and without halothane, could be defined while controlling many of the above factors.

Inhaled anesthetics alter vascular tone and inhibit HPV (1,2). Several studies support the idea that inhaled anesthetics alter the release of eicosanoids by the pulmonary circulation in response to various stimuli, including hypoxia (6,8,10). These studies used organ systems and demonstrated prostanoid involvement by cyclooxygenase blockade; however, the source of these prostanoids could not be identified. The present study supports and extends these results by demonstrating that halothane increased eicosanoid release by perfused pulmonary endothelium. These data are consistent with modulation of endothelial eicosanoid release as a mechanism by which anesthetics could affect vessel tone and blunt HPV. Eicosanoids other than 6-keto $PGF_{1\alpha}$ were assayed to elucidate the spectrum of eicosanoid metabolism rather than only cyclooxygenase-dependent activity. The increase in all eicosanoids suggests an anesthetic effect proximal to cyclooxygenase in arachidonate metabolism. Inhaled anesthetics are known to interact with cell membranes (31). Potentially, anesthetics could alter endothelial arachidonate metabolism, which occurs in the lipid bilayer of cell membranes. Both prostaglandin and LT release were increased by halothane, indicating increased activity in both cyclooxygenase and lipoxygenase, and may cause arachidonate release from the cell membrane phospholipids, perhaps by increased phospholipase A_2 activity (13).

In this study, the endothelial release of eicosanoids was determined at two oxygen tensions that resulted from equilibrating perfusate with a normoxic (fraction of inspired O_2 [FIO_2] 0.21) and hypoxic (FIO_2 0.04) gas mixture. Although a PO_2 of 50 mm Hg is physiologic in the main pulmonary artery, a perfusate PO_2 of 50 mm Hg was selected because at this oxygen tension, the pulmonary vascular response to hypoxia is maximal (11). Prostacyclin release by perfused endothelial cells was acutely increased by hypoxia, and this response was sustained over 3 h (Table 2). These results are consistent with intact animal and isolated perfused lung studies (32–34) but differ from previous results in static cell populations exposed to acute and chronic hypoxia (15,16,35). These results underline the importance of perfusion as a factor in endothelial cell function. Halothane increased prostacyclin release similarly during both normoxia and hypoxia.

Several studies have reported conflicting conclusions concerning the role of thromboxane in HPV (17,36,37). Inhibitors of thromboxane synthetase did not prevent HPV in isolated, perfused rat lungs (37).

However, thromboxane was implicated in pulmonary venous constriction during hypoxia in isolated, perfused lamb lungs (36). Farber et al. (17) showed a transient elevation in thromboxane release during acute hypoxia using a static endothelial cell culture model. In our study, hypoxia did not alter thromboxane release, which implies that endothelial thromboxane release is unlikely to be involved in the pulmonary vascular response to hypoxia. Halothane increased TXB_2 release, but the release rate was quite low.

Numerous studies have reached conflicting conclusions concerning LT involvement in HPV (36,38–42). Leukotriene antagonists, as well as LT synthesis and receptor blockers, have been reported to inhibit HPV (38,39). In contrast, other studies have shown no role for LTs in HPV (40–42). These studies are complicated by the presence of multiple cell types (mast cells, leukocytes, platelets) that all potentially produce LTs in response to hypoxia. Leukotriene assays are problematic, due in part to the presence of protein in serum-containing media. In this study, the perfusate was a protein-free, buffered crystalloid solution. Although endothelium is not recognized as a significant source of LTs, isolated endothelial cells have been shown to possess lipoxygenase activity (43,44). The present study investigated total peptidoleukotriene release in isolated, perfused endothelial cells, which has not previously been (specifically) investigated. By assaying for total peptidoleukotriene production, as opposed to each peptidoleukotriene individually, the amount released may have been sufficient to be measurable. In addition, perfusion may have provided the shear stress to the lipid cell membrane that is necessary for measurable peptidoleukotriene production. Nevertheless, this release was not altered by hypoxia. Therefore, endothelial peptidoleukotriene release seems unlikely to mediate HPV.

Halothane increased the release of all assayed eicosanoids during both normoxia and hypoxia. In vivo, the local concentrations of endothelial eicosanoids and the response of the subjacent vascular smooth muscle determine the physiologic response. Because the relationship of the release rates in this system to in vivo eicosanoid concentrations is unknown, application of these data is largely qualitative. Prostacyclin is a potent pulmonary vasodilator and inhibits HPV (13). The effect of peptidoleukotrienes is less clear. Although in some species peptidoleukotrienes are pulmonary vasoconstrictors, in others, including cows, primates, and humans, they have little effect (45,46). In these species, the increased endothelial peptidoleukotriene release with halothane is unlikely to have any significant vascular effect. The release of TXB_2 is an order of magnitude less than that of prostacyclin and the LTs, and therefore its effect would be much less significant. For these reasons, it seems likely that the net vascular effect of increased endothelial eicosanoid release by halothane seen in this study would be decreased PVR, especially when PVR is elevated, as, for example, by hypoxia.

In conclusion, hypoxia stimulated endothelial prostacyclin release, consistent with endothelial attenuation of HPV by altered eicosanoid release. Halothane increased pulmonary endothelial eicosanoid release during both normoxia and hypoxia. Altered endothelial eicosanoid release may be an important mechanism by which halothane modulates vascular tone.

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Acute Toxic Delirium in a Patient Using Transdermal Fentanyl

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Recent advances in transdermal drug systems permit continuous delivery of medications to patients for a variety of indications. The development of such a system for fentanyl (Duragesic, Janssen Pharmaceutica) has greatly expanded the use of systemic fentanyl for patients with chronic pain. Using this device, serum concentrations of fentanyl reach a plateau after approximately 18 h and tend to remain stable thereafter (1). Few complications have been reported, of which nausea and somnolence are the most common (1,2). We report a case of acute toxic delirium in a patient who used transdermal fentanyl patches for 24 days.

Case Report

A 71-year-old woman with squamous cell carcinoma had undergone a hemimandibulectomy followed by maximal radiation therapy. She lived alone and was stable until 2 wk before admission, when she sought relief of increasing jaw pain. She was given a Duragesic 25-μg/h patch. When her pain persisted the next day, she was switched to a 50-μg/h patch and told to increase her dose by 25 μg/h once daily until pain control was achieved. Four days before admission, she again complained of pain despite the use of 125 μg/h of transdermal fentanyl. The next day, she began to hallucinate, and her family described her as having become delusional. Admission was arranged.

On the day of admission, the patient was using two 50-μg/h Duragesic patches and one 25-μg/h patch. The next day, she was given one tablet of 60-mg sustained-release morphine sulfate. On the third day, she said, "This is some kind of trick." She was confused during the evening, asking for breakfast and trying to get up to go home. Lorazepam (0.5 mg orally) was given at bedtime. On the fourth day, the transdermal fentanyl patches were replaced, and she was also given three doses of 60-mg sustained-release morphine sulfate during the day and an evening dose of lorazepam (0.5 mg). She appeared restless and spent the entire night pacing her room, confused and agitated. On the fifth day, she remained confused, agitated, and paranoid despite four doses of lorazepam (0.5 mg) and two 60-mg morphine tablets during the day. On the sixth day, the same pattern continued, despite the addition of haloperidol (0.5 mg) given by mouth. Serum concentrations of sodium, potassium, magnesium, calcium, vitamin B_{12}, and folate were normal; the urea nitrogen and creatinine concentrations were 44 and 2.2 mg/dL, respectively. A computed tomography scan of the head was essentially normal. She remained confused and agitated on hospital days 7–9. On the ninth day, psychiatric consultation was requested after full-time sitters were required, despite daily doses of haloperidol (up to 9 mg on day 9). The transdermal fentanyl patches, 100 and 25 μg/h, had been replaced on day 7.

Psychiatric assessment on day 9 revealed an elderly, cachectic woman standing beside her bed, picking aimlessly at the bedclothes. She had been incontinent of stool. Pupils were pinpoint. She was able to give only one- or two-word responses. She was oriented to the year but not to month, date, or place. She was able to name her daughter and sister (they were present in the room) but could not describe their relationships correctly. She was uncooperative with further mental status examination. Her affect was flat, and she was in no obvious pain. The psychiatrist diagnosed toxic delirium.

On the tenth hospital day, the transdermal fentanyl patches were removed, and intravenous morphine at 4 mg/h was begun. The next day the patient was dozing comfortably, able to ambulate with assistance to the toilet, and began to take fluids by mouth. She was no longer combative and denied experiencing pain. Her mental state improved so that sitters and antipsychotic medications were discontinued. She was maintained on modest doses of intravenous and oral morphine and required only general supportive care until her discharge to an extended care facility on hospital day 28. During this time, she was alert and oriented, reading books, listening to the radio, and visiting with family members.

Discussion

Fentanyl is a phenylpiperidine derivative, structurally related to meperidine. Like meperidine, it can be

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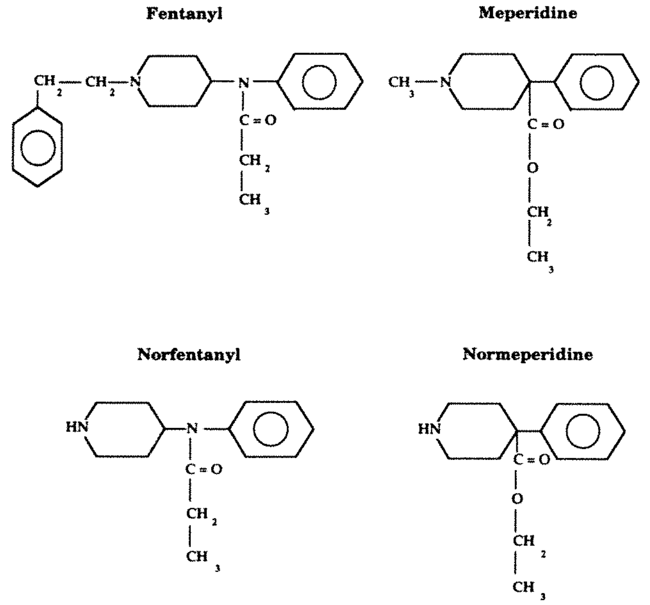

Figure 1. Chemical structures of fentanyl, norfentanyl, meperidine, and normeperidine. The structural similarity of norfentanyl to normeperidine is easily seen.

metabolized by *N*-demethylation, producing norfentanyl, which is structurally similar to normeperidine (Figure 1). Norfentanyl may be the principal metabolic degradation product of fentanyl in humans (3–5). It is excreted by the kidney and can be detected in the urine 72 h after a single intravenous dose of fentanyl (3). Animal studies suggest that norfentanyl has less analgesic potency than fentanyl (4). No detailed pharmacokinetic data or information concerning its physiologic effects in humans appears in the literature.

Normeperidine can accumulate in the serum and cause a variety of adverse effects in patients taking repeated doses of meperidine (6–8). Its serum half-life of 15–30 h is prolonged in patients with diminished renal function (6,7). Normeperidine appears to have antianalgesic properties and has been associated with negative mood alterations. It can cause a variety of central nervous system excitation effects, including tremors, myoclonus, and grand mal seizures (6,8). These adverse effects cannot be reversed with naloxone (6).

We suspect that norfentanyl began to accumulate in this patient's serum, perhaps accelerated by her advanced age, general debility, and renal insufficiency. The effects of age on fentanyl pharmacokinetics remain unclear. Singleton et al. (9) found that the clearance and elimination half-life of intravenous fentanyl in healthy elderly persons was the same as in a younger group. Two reports suggest that the elimination half-life of fentanyl in healthy adults after transcutaneous administration for 1 day is 16–21 h (10,11). Esteve et al. (12) confirmed this result in a group aged 30–65 yr but found that older patients (78–88 yr; $n = 6$) had an elimination half-life of 43 h. The effect of age, if any, on the clearance of norfentanyl is unknown. The potential actions of norfentanyl, toxic or otherwise, remain speculative; however, its structural similarity to normeperidine raises the possibility that it has similar physiologic effects. If so, it may have been responsible for the excitation and narcotic resistance demonstrated by our patient.

There are a number of other potential causes for this patient's delirium. Persons receiving potent opiates may experience a variety of subjective effects, including hallucinations and delirium. Such paradoxical reactions usually occur shortly after the opiate is administered and can be reversed with naloxone. A literature search revealed a single case report of acute delirium that occurred after intravenous administration of fentanyl (100 μg) (13). This patient's mental status returned to normal shortly after she received naloxone. Another report describes a case in which acute delirium followed general anesthesia during which the patient also received droperidol and epidural fentanyl. In this instance, no naloxone was administered, and the patient recovered gradually over 2 days (14). We also cannot exclude with certainty the possibility of an adverse reaction to one of her other medicines as a cause of her altered sensorium. However, all of these, except the transdermal fentanyl patch, were continued after the resolution of her delirium. The list of potential side effects of Duragesic noted in the package insert includes hallucinations, agitation, abnormal thinking, and paranoid reaction. However, the manufacturer was unable to provide any specific case histories to support this information (I.H. White, personal communication), and no published reports link transdermally administered fentanyl to these side effects.

Large doses of opiates may cause hypoventilation and hypoxemia, although this usually coincides with clinically obvious sedation. Hypoxemia occasionally presents as confusion. Neither arterial blood gases nor hemoglobin saturation was measured directly in this case, but the patient had normal pulmonary function and remained alert and active, even agitated, throughout the period of her confusion. She continued to complain of pain before her admission, despite the use of transdermal fentanyl (125 μg/h). The addition of up to 120 mg/day of oral morphine did not fully relieve her discomfort. This represents an opiate dose equivalent to more than 14 mg/h of morphine. In the subsequent absence of fentanyl, she remained comfortable while receiving only intravenous morphine at 4–5 mg/h. The absence of effective pain control and the clinical picture of an active patient suggest that opiate overdose with respiratory depression was not the major issue. It is unfortunate that this impression was not confirmed by a blood gas measurement.

In summary, we present a patient with renal insufficiency who experienced poor pain control and developed an acute toxic delirium while receiving transdermal fentanyl in doses of up to 125 μg/h. One day after the fentanyl patch was removed, her pain could be controlled with intravenous morphine at 4–5 mg/h, and her mental status abnormalities resolved without specific treatment. We suspect that accumulation of norfentanyl in her serum caused her narcotic resistance and delirium.

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Prolonged Hypotension by Enalaprilat in a Case of Renal Artery Stenosis

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The use of angiotensin-converting enzyme (ACE) inhibitors has been a major advance for the treatment of both hypertension and congestive heart failure. Moreover, the introduction of the intravenous preparation enalaprilat has expanded the use of these drugs to the intraoperative and perioperative periods (1–3). As with outpatient use, however, intraoperative complications, such as severe hypotension or acute renal insufficiency, or both, may be seen when these drugs are used in the setting of high renin states such as renal artery stenosis (4,5). We describe a case of significant and prolonged hypotension associated with the intraoperative use of intravenous enalaprilat in a patient with undiagnosed renal artery stenosis. In retrospect, the severity of the complication confirms the dangers associated with ACE inhibitor use in conditions that constitute contraindications.

Case Report

The patient was a 36-yr-old, 98-kg, 155-cm woman admitted for lumbosacral vertebral decompression with Steffe instrumentation due to degenerative spine disease and segmental instability of segments L1–S1. Her past medical history was significant for a recent 4-mo history of diastolic hypertension (95–110 mm Hg) treated with alterations in diet and with diuretic therapy. The patient also admitted to cigarette smoking and a strong family history of hypertension. Preoperative physical examination was unremarkable except for moderate obesity. Arterial blood pressure was measured at 134/95 mm Hg (mean arterial pressure [MAP] 108 mm Hg) and heart rate at 90 beats/min. Serum potassium concentration was 3.6 mEq/L, and hematocrit was 36% (after predonation of two autologous whole units of blood).

The patient was first seen the morning of surgery, at which time she was given her diuretic (chlorothiazide, 500 mg by mouth) and midazolam (0.05 mg/kg intramuscularly). Before induction of anesthesia, electrocardiogram (leads II and V_5), digital pulse oximeter, radial artery, and central venous pressure monitoring were established. Anesthesia was induced with thiopental (5 mg/kg IV), droperidol (0.625 mg IV), and sufentanil (0.5 $\mu g/kg$ IV), and tracheal intubation was facilitated by administration of doxacurium (0.08 mg/kg IV). Radial artery blood pressure increased to 190/120 mm Hg (heart rate 122 beats/min) after tracheal intubation and was treated successfully with isoflurane, 2.0% inspired in oxygen, and an additional dose of sufentanil (0.25 $\mu g/kg$ IV). After insertion of an indwelling urinary catheter, the patient was positioned prone for surgery, ensuring an uncompressed abdomen and proper limb support. Anesthesia was maintained with sufentanil (0.25 $\mu g \cdot kg^{-1} \cdot h^{-1}$ IV) and 0.5% isoflurane inspired in a 70%/30% mixture of N_2O/O_2, with additional bolus doses of doxacurium (0.01 mg/kg) as needed for surgical relaxation. Ventilation was controlled mechanically and monitored capnographically.

On incision, the radial artery pressure was measured at 160/105 mm Hg (MAP 123 mm Hg), heart rate at 82 beats/min, and central venous pressure (CVP) at 6 mm Hg. In an attempt to minimize blood loss and facilitate surgical exposure, a MAP of 75–80 mm Hg was chosen to be achieved by a combination of increasing concentrations of isoflurane and sodium nitroprusside (SNP). Approximately 45 min after incision, and immediately before osteotomy, arterial blood pressure remained at 155/92 mm Hg (MAP 113 mm Hg), with a heart rate of 99 beats/min despite an isoflurane concentration of 3.0% and an infusion of SNP of 2.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$. The CVP was 9 mm Hg, and urine flow was >1.0 $mL \cdot kg^{-1} \cdot h^{-1}$. As progressively higher infusion rates of SNP failed to significantly affect the MAP (to a dosage of 6.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$), 0.625 mg of intravenous enalaprilat was administered as a third antihypertensive drug. Commencing approximately 10 min after administration, radial artery blood pressure diminished gradually. Within 20 min after enalaprilat administration, however, arterial blood pressure decreased to 65/32 mm Hg (MAP 43 mm Hg), with a heart rate of 79 beats/min despite withdrawal of the SNP and sufentanil infusions and isoflurane, as well as irrigation and packing of the wound by our surgical colleagues. Ventilation was controlled with 100% inspired oxygen. End-tidal CO_2 concentrations decreased from 36 to 25 mm Hg, and CVP diminished to 2 mm Hg. No air could be aspirated from the central venous catheter nor were murmurs heard through an esophageal stethoscope. The position of the abdomen

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was examined for unusual compression or rotation from the initial prone position, although without comment. Radial artery pressure was increased with significant difficulty to 112/64 mm Hg (MAP 80 mm Hg) and CVP to 11 mm Hg with aggressive intravenous crystalloid and hetastarch resuscitation (3 and 1 L, respectively) and increment boluses of ephedrine (5 mg IV) and phenylephrine (50 μg IV), thus allowing reinstitution of the anesthetic and resumption of surgery. Urine output remained >1.0 mL·kg^{-1}·h^{-1}, and arterial blood gases revealed a lowest base deficit of -1.2 mEq. Surgery and anesthesia were completed without incident thereafter, with an estimated total blood loss of 650 mL.

Within the first 5 days postoperatively, the patient remained stable, except for consistent diastolic hypertension (110 mm Hg) and a slight increase in the serum creatine level (0.8 to 1.1 mg/dL). Within 1 mo of surgery, owing to her history of hypertension along with recent intraoperative events, the patient underwent an intravenous pyelogram and technetium DTPA (renal) scan that revealed a small, atrophic right kidney with poor uptake (respectively) as opposed to a slightly larger than normal left one with good isotope uptake. Differential renal vein renin determinations revealed a wide disparity between the opposing kidneys (16.2 ng·mL^{-1}·h^{-1} right; 2.8 ng·mL^{-1}·h^{-1} left). Eventual arteriography demonstrated a 95% luminal narrowing of the right renal artery, consistent with fibromuscular dysplasia. The patient underwent successful transluminal balloon dilation of the stenosis shortly thereafter, with resolution of her diastolic hypertension within the following 48 h.

Discussion

Renovascular hypertension resulting from renal artery stenosis accounts for up to 5% of the hypertension seen in the general population (6). Fibromuscular dysplasia of the renal arteries accounts for about one-fourth of all cases of renovascular hypertension, most commonly affecting young women (7). Atheromatous disease, on the other hand, constitutes the bulk of the remaining majority, although it most often afflicts older individuals with risk factors for (or known) atheromatous disease elsewhere.

The diagnosis of renal artery stenosis, and in particular fibromuscular dysplasia, requires a high index of suspicion and is often considered in the young, otherwise healthy, woman with severe diastolic hypertension (>110 mm Hg) (8). It can be argued that such a diagnosis should have been entertained preoperatively in our patient, although the combination of documented moderate diastolic hypertension (95–110 mm Hg) and a host of risk factors for essential hypertension (obesity, smoking, family history) incorrectly led to that diagnosis. This, unfortunately, is not uncommon. In fact, large series using arteriography in patients with risk factors for essential hypertension have detected some degree of renal artery stenosis in 32% of the normotensive patients and in 62% of the hypertensive patients in such series, which may or may not have contributed to the hypertension in the latter group (9).

It is interesting to note that arterial blood pressure responses to ACE inhibitors, and in particular captopril, have been used to diagnose renovascular disease despite evidence of poor sensitivity and specificity. Better established, though, is the good correlation between the hypertension control from long-term use of ACE inhibitor therapy and predictions of the surgical curability of renovascular hypertension (10,11). This "hypotensive" response is largely due to blunting of angiotensin II production from the stenotic kidney (secreting the majority of renin), with significant reductions in vascular resistance and, subsequently, arterial blood pressure. Our patient exhibited profound, refractory hypotension in conjunction with enalaprilat use, most likely due to the dangerous combination of high doses of two vasodilators and (relative) hypovolemia, the latter being unmasked by the inhibition of the chronic production of the vasoconstrictor angiotensin II. That the renin-angiotensin system, in addition, plays a role in the maintenance of blood pressure during anesthesia, including isoflurane anesthesia, may have contributed to the hypotension seen with use of the ACE inhibitor as well (12).

The hypertensive responses seen in our patient during anesthesia and surgery, despite what was judged to be an adequate depth of anesthesia, are entirely consistent with secondary forms of hypertension such as renal artery stenosis. Our attempt to decrease MAP, to facilitate surgical exposure and minimize blood loss, by the administration of an ACE inhibitor (as opposed to a β-adrenergic blocker or other antihypertensive drug) is entirely consistent with previous work (13,14). Administration of ACE inhibitors has been associated with significantly lower doses of SNP used to achieve deliberate hypotension as well as diminished plasma cyanide levels during SNP use. Although we did not suspect cyanide toxicity in our patient nor determine cyanide levels, the maximal dosage used (6.1 μg·kg^{-1}·min^{-1}) did approach recommended safe guidelines for administration (8.0 μg·kg^{-1}·min^{-1}).

We should note that at present, enalaprilat lacks Food and Drug Administration approval for use in deliberate hypotension, although its use is appropriate in cases of resistant hypertension seen perioperatively or otherwise.

It is certainly possible that etiologies other than enalaprilat administration, such as unrecognized hemorrhage, positioning errors, or air embolism, were responsible for the rather precipitous hypotension seen in this case. We believed, as did our surgical colleagues, however, that the former two reasons were satisfactorily ruled out. Although we could not definitely rule out the presence of air embolism as a cause of the hemodynamic collapse because our end-tidal CO_2 levels did decrease and we had not used end-tidal nitrogen or Doppler techniques in this case, our suspicions were minimized because of the lack of aspiration of air through the central venous catheter, the low CVP reading itself, and the modest accumulation of blood in the wound before the event. We eventually attributed the lowered end-tidal CO_2 measurements to poor pulmonary blood flow associated with the hypotension.

Of importance, the time frame involved from administration of intravenous enalaprilat to the hypotension is entirely consistent with the pharmacokinetics of the drug given its onset of approximately 15 min and peak effect of 30 min (15). In addition, enalaprilat, in doses as low as 0.5 mg IV, completely inhibits ACE activity for ≥60 min (3) and may explain the difficulty we experienced when attempting to increase our patient's blood pressure. The heart rate of 79 beats/min during the event, which was less than expected or previously recorded, especially in the absence of β-adrenergic blockade, is also consistent with the effects of the ACE inhibitor (16). This lack of reflex tachycardia, unlike the increases in heart rate seen with other afterload reducers, has yet to be adequately explained, although enhancement of parasympathetic activity (or disinhibition) (17) and a drug-induced venodilatory action have been suggested (18).

Although this case should serve to heighten our suspicion of renovascular disease in our patient's subgroup, it most importantly demonstrates the potential dangers of ACE inhibitor use, especially in conjunction with other potent vasodilators also used during anesthesia. Profound hypotension, associated with the use of these drugs, has also been reported intraoperatively as well as postoperatively, although often for reasons unknown at the time (19,20). Moreover, as our patient had unilateral renal artery stenosis with a normal contralateral kidney, the likelihood of acute renal failure precipitated by enalaprilat use was small. However, in patients likely to benefit from use of ACE inhibitors, specifically those with hypertension and concomitant peripheral vascular disease, the incidence of undetected, bilateral renal artery stenosis may be as high as 12% (21). Such patients may have a dramatic decrease in glomerular filtration rate and renal function as a result of ACE inhibitor therapy (4). This decrease in glomerular filtration rate is attributed to blunting of angiotensin II-mediated efferent arteriole constriction necessary to maintain glomerular capillary perfusion in patients with bilateral renal artery stenosis or stenosis in a solitary kidney (22). These conditions, as well as those of low intravascular volume, abnormal electrolyte status (i.e., hyponatremia), and effects of other vasoactive drugs, should be very familiar to the clinician before the consideration of administration of any ACE inhibitor.

In summary, we report a case in which unexpected and severe hypotension from intravenous enalaprilat use occurred in a patient with undiagnosed renal artery stenosis. It is hoped that this discussion will help more clearly define the appropriate guidelines for use of ACE inhibitors in the intraoperative and perioperative periods.

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Electroencephalographic Monitoring of Cerebral Function During Asystole and Successful Cardiopulmonary Resuscitation

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Previous studies have documented changes in the electroencephalogram (EEG) that occur secondary to cerebral ischemia (1–3). During periods of complete global ischemia, such as occur after cardiac arrest, cerebral blood flow ceases. The functional (electrical) activity of the cerebral cortex, as monitored by the EEG, is abolished as a result of compromised cerebral oxygenation. Initially, there is a reduction in the high-frequency component of the EEG with an apparent increase in the low-frequency component; soon thereafter, the EEG becomes isoelectric. In a patient with generalized EEG suppression that occurs secondary to cardiac arrest, it is appropriate to assume that cerebral oxygenation due to cardiopulmonary resuscitation (CPR) is adequate in the setting of EEG recovery. In this setting, EEG changes associated with cardiac arrest and CPR are of significance.

Using seven-channel EEG monitoring in a patient undergoing carotid endarterectomy, Moss and Rockoff (4) described the changes in EEG activity that occurred during a brief period (27 s) of ventricular asystole and the prompt return of EEG activity with restoration of intrinsic cardiac rhythm and blood pressure. Using compressed spectral-array EEG monitoring in a patient undergoing carotid endarterectomy, Young and Ornstein (5) described the changes in spectral edge frequency during cardiac arrest and CPR. As pointed out by these authors, because they lacked a concurrent display of the raw EEG, they could not separate artifact from EEG activity during the time of resuscitation.

Neither of these cases describe changes in the raw EEG during manual chest compressions. We describe here a case of intraoperative cardiac arrest (of approximately 2-min duration) and the resulting changes in the raw EEG signal after initiating manual chest compressions and CPR in a patient undergoing carotid endarterectomy. This case demonstrates the time-course for EEG activity to return when effective manual chest compressions are initiated soon after cardiac arrest occurs. Additionally, this case suggests that EEG monitoring of cerebral function can provide useful information with regard to the adequacy of cerebral oxygenation during manual chest compressions and CPR in anesthetized patients experiencing cardiac arrest.

Case Report

A 72-yr-old man experienced several episodes of left hemispheric transient ischemic attacks. Carotid angiography revealed >95% stenosis of the left internal carotid artery, <15% stenosis of the right internal carotid artery, and filling of the left middle cerebral artery distribution during injection of the right carotid artery. The patient was scheduled to undergo a left carotid endarterectomy.

Past medical history was remarkable for chronic atrial fibrillation and non-insulin-dependent diabetes mellitus. The patient denied a history of angina or previous myocardial infarction. Preoperative echocardiography revealed an ejection fraction of 58% without regional wall motion abnormalities. Medications included digoxin and micronase. Preoperative electrocardiogram (ECG) was remarkable for atrial fibrillation with a ventricular rate of 78 beats/min and nonspecific ST-T wave abnormalities. The ECG was unchanged compared with an ECG obtained 3 yr earlier. Preoperative laboratory values revealed hemoglobin 14.8 g/dL, serum potassium 4.1 mEq/L, glucose 157 mg/dL, and digoxin 1.2 ng/mL (normal 0.5–2.0 ng/mL). Preoperative arterial blood pressure and heart rate ranged from 110/60 to 120/80 mm Hg and from 65 to 85 beats/min, respectively. The patient did not experience symptoms of cerebral ischemia within this blood pressure range during his 4 days of hospitalization before surgery.

On physical examination, there was no detectable neurologic deficit on the morning of surgery. Intraoperative monitoring included a blood pressure cuff, five-lead ECG, pulse oximeter, indwelling radial artery catheter, esopha-

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geal stethoscope, esophageal temperature probe, peripheral nerve stimulator, mass spectrometer, and continuously monitored 16-channel EEG. Before the administration of any anesthetics, a baseline EEG was obtained. The baseline EEG was symmetric and without focal abnormalities suggestive of cerebral ischemia or infarction. After preoxygenation, anesthesia was induced with intravenous propofol (1.3 mg/kg) and fentanyl (2.7 μg/kg). Vecuronium (0.2 mg/kg IV) was administered to facilitate laryngoscopy and tracheal intubation. Anesthesia was maintained with a continuous infusion of propofol (30–70 $\mu g \cdot kg^{-1} \cdot min^{-1}$) and 50% N_2O in O_2. Blood pressure was maintained between 110/60 and 140/80 mm Hg, with a phenylephrine infusion as needed.

During surgical manipulation of the carotid artery, but before the endarterectomy, the patient's heart rate, which had ranged between 50 and 60 beats/min suddenly decreased and progressed to asystole <10 s later. The surgeons immediately discontinued manipulation of the carotid artery, but cardiac rhythm failed to return. Administration of propofol and N_2O was discontinued, the lungs were ventilated with 100% O_2, atropine (0.8 mg IV) was administered, and manual chest compressions were begun simultaneously. Epinephrine (1.0 mg IV) was administered soon thereafter, because no intrinsic cardiac rhythm could be detected when chest compressions were temporarily suspended.

Continuous recordings of the 16-channel EEG (longitudinal bipolar montage) were obtained immediately before, during, and after the period of asystole (Figure 1). Approximately 10 s after the onset of asystole, there was generalized suppression on the EEG that progressed to near isoelectricity soon thereafter. With institution of manual chest compressions, low-voltage high-frequency activity began to return approximately 15–20 s later. During pauses in CPR to assess the presence or absence of cardiac rhythm, low-voltage high-frequency activity was evident in most channels without gross asymmetry in EEG activity between corresponding channels of the left and right cerebral hemispheres. After the return of cardiac rhythm and termination of CPR, the EEG appeared similar to the recording obtained immediately before cardiac arrest.

Cardiac rhythm was not detected until approximately 2 min after the onset of asystole, at which time sinus tachycardia (heart rate increased to 180 beats/min) and systemic hypertension (arterial blood pressure increased to 220/120 mm Hg) developed. Intravenous esmolol, in 0.5-mg/kg increments, and a continuous infusion of nitroprusside were temporarily used to control heart rate and arterial blood pressure until the hemodynamic effects of the epinephrine subsided.

Hemodynamics stabilized, and the decision was made to proceed with the endarterectomy after infiltrating the carotid sinus with 2 mL of 2% lidocaine to prevent further episodes of bradycardia and asystole during carotid manipulation. Anesthesia was maintained with propofol and N_2O, and the endarterectomy was performed without further incident. The patient emerged from general anesthesia without a neurologic deficit and remained neurologically and hemodynamically stable throughout the perioperative period. The patient was discharged to home on the eighth postoperative day with normal neurologic function.

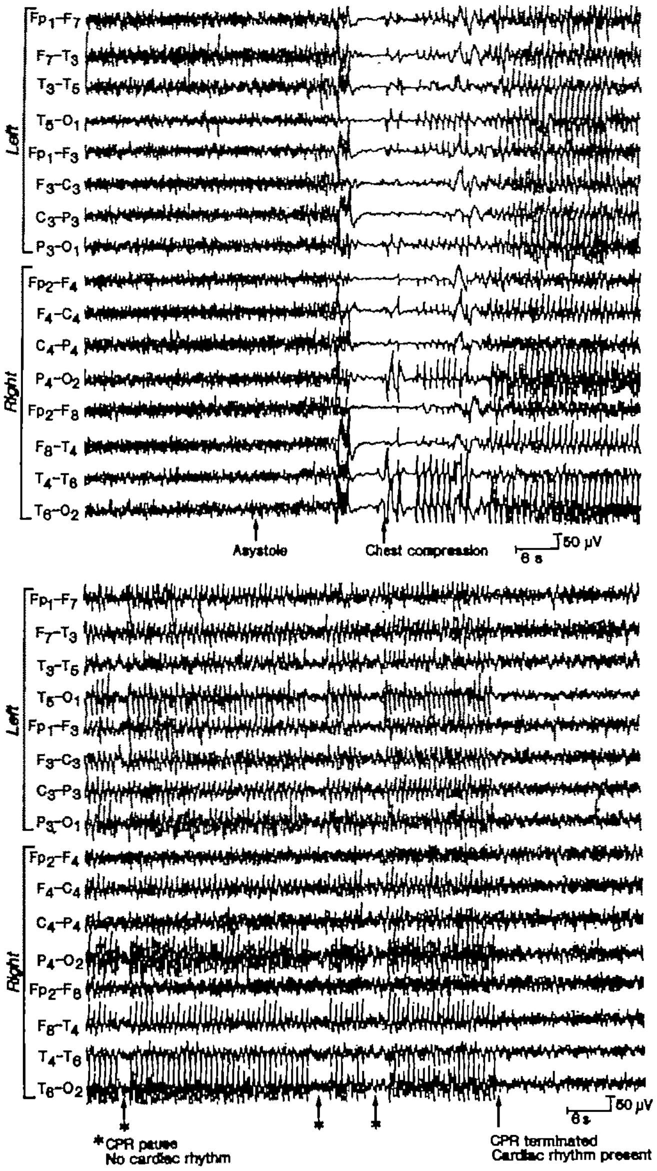

Figure 1. Continuous recordings of the 16-channel EEG obtained immediately before, during, and after the period of asystole. **Top.** Approximately 10 s after the onset of asystole, there was generalized suppression on the EEG, progressing to near isoelectricity soon thereafter. Manual chest compressions are responsible for the EEG artifact (biphasic spikelike activity) that is evident in most channels of the EEG. Amid this artifact, low-voltage high-frequency activity began to return approximately 15–20 s after initiating manual chest compressions. **Bottom.** Chest compressions were temporarily suspended to assess cardiac rhythm. In the absence of EEG artifact during these periods, low-voltage high-frequency activity is evident in most channels without gross asymmetry in EEG activity between corresponding channels of the left and right hemispheres. After the return of cardiac rhythm and the termination of chest compressions, the EEG appears similar to that observed immediately before the onset of asystole. CPR, cardiopulmonary resuscitation.

Discussion

We describe a patient who developed diffuse EEG slowing and suppression within 10–20 s after asystole occurred. This is consistent with experimental data in primates and humans. In a primate study of complete cerebral ischemia, the mean time to development of an isoelectric EEG was approximately 10–15 s (6). Similarly, after brief cardiac arrest in humans, the mean time to onset of EEG changes was approximately 10 s (7).

In the absence of specific measurements, such as regional cerebral blood flow, cerebral metabolites, or cerebral tissue acid-base status, it is not possible to eliminate the possibility that some degree of cerebral ischemia occurred during CPR. However, despite the amount of EEG artifact produced by chest compressions as well as the brief duration of CPR pauses during which time this artifact was absent, it is clear that low-voltage high-frequency activity was present in most, if not all, channels of the EEG during CPR. In addition, no channel demonstrated predominant slow-wave activity or complete absence of electrical activity, as would be expected to occur in the setting of severe cerebral ischemia. After the return of cardiac rhythm and arterial blood pressure, there was no evidence of gross cerebral cortical dysfunction on the EEG, because it appeared similar to the recording obtained immediately before the cardiac arrest.

Using a compressed spectral array, Young and Ornstein (5) observed a transient reduction in spectral edge frequency immediately after successful CPR in a patient undergoing carotid endarterectomy. With time, spectral edge frequency gradually increased toward the prearrest value. The authors speculated that transient cerebral ischemia may have been responsible for this observation, although the period of cerebral ischemia should have been brief. When CPR was terminated in our patient, there were no changes indicative of cerebral ischemia on the EEG. This suggests that cerebral oxygenation was adequate at this time and that if some degree of cerebral ischemia did occur during CPR, it must have been brief or mild, or both.

In our patient, high-frequency activity began to return to the EEG approximately 15–20 s after CPR was initiated. The return of this activity signaled the return of cerebral perfusion and oxygenation. The speed with which EEG activity returned was similar to that with which EEG activity was lost after the onset of asystole. It is likely that several factors are responsible for the rapid return of EEG activity after CPR was initiated. First, CPR was initiated soon after asystole occurred, thus preventing a prolonged episode of cerebral ischemia. Second, it is likely that well-oxygenated blood was essentially "standing by" in the arterial circulation and that restoration of cerebral blood flow with manual chest compressions quickly restored cerebral oxygenation, as evidenced by the rapid return of EEG activity.

Although it is appropriate to assume that cerebral oxygenation is adequate in the setting of EEG recovery, one cannot assume that the absence of EEG recovery would indicate poor CPR and cerebral oxygenation. Recovery of EEG activity depends on both the magnitude and duration of the ischemic episode as well as on the efficacy of CPR. Thus, it would have been possible to have a much longer period of ischemia before initiating CPR, with equivalently effective CPR during the resuscitation period, and have minimal or no recovery of EEG activity owing to the magnitude of the ischemic insult.

It is interesting that in this patient with a critical carotid stenosis there was no gross asymmetry evident on the EEG during manual chest compressions and CPR. As demonstrated on the preoperative angiogram, the patient had a hemodynamically insignificant atherosclerotic lesion (15% stenosis) of the right internal carotid artery with filling of the left middle cerebral artery distribution during injection of the right carotid artery. Therefore, although the patient had a >95% stenosis of the left internal carotid artery, blood was being supplied to the left cerebral hemisphere in the distribution of the left middle cerebral artery from the right internal carotid artery through the circle of Willis. Similar to the description of cerebral blood flow evident on the preoperative angiogram, during manual chest compressions and CPR, blood flow and oxygen supply to the cerebral hemisphere ipsilateral to the carotid stenosis were probably via the contralateral internal carotid artery and circle of Willis. The observation that asymmetric EEG changes of cerebral ischemia were notably absent during CPR probably relates to the fact that the right internal carotid artery and circle of Willis provided an essentially disease-free route for blood flow and oxygen delivery to the left cerebral hemisphere during manual chest compressions and CPR.

In conclusion, the 16-channel EEG can be a useful monitor of cerebral perfusion and oxygenation during CPR, because it provides a functional assessment of the cerebral cortex. Use of EEG monitoring during CPR, although not allowing us to rule out the presence of a small ischemic insult, did provide us with reassurance that manual chest compressions were effective and that there were sufficient cerebral perfusion and oxygenation to restore the electrical activity of the cerebral cortex after a brief period of EEG suppression.

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Chiari I Malformation Presenting as Recurrent Spinal Headache

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Postdural puncture headache (PDPH) is a well-recognized complication after spinal anesthesia (1). When conservative treatment or epidural blood patch (EBP) fail, alternative causes of the headache need to be reconsidered. We present a previously unreported association of recurrent PDPH with a Chiari I malformation.

Case Report

A 31-yr-old woman (gravida 1, para 0), with an unremarkable medical history, received analgesia for labor via a lumbar epidural catheter. Subsequently, when she required cesarean section for failure of the labor to progress, satisfactory lumbar epidural anesthesia could not be established. Good surgical anesthesia was provided by subarachnoid block, although spinal needle placement proved technically difficult and required several attempts before successful dural puncture with a 22-gauge needle. The surgery and immediate postoperative period were uneventful. Although she reported a mild positional headache, her surgeon discharged her on the third postoperative day. However, over the following several days, the patient's headache became progressively more severe. The headache was associated with mild neck pain, which worsened when the patient was sitting or standing. Moderate relief was obtained by caffeine ingestion. On the sixth postoperative day, although afebrile, she developed hearing changes (echoing), visual disturbances (blurring and color distortion), and nausea. The diagnosis of PDPH was made. An EBP using 15 mL of autologous blood was administered, with marked improvement of all symptoms.

The patient had a recurrence of the headache 4 days later. The headache was similar in character to the original, but the severity had increased, causing her to awaken at night. In view of these symptoms, neurologic consultation was obtained before consideration was given to a repeat EBP. Although the physical examination was normal, a magnetic resonance imaging scan was ordered, which revealed a Chiari I malformation. During the recommended treatment of a 6-wk course of prednisone, her symptoms progressively improved, and she remains symptom free.

Discussion

The Chiari I malformation consists of displacement of the tonsils of the cerebellum through the foramen magnum and, possibly, into the cervical spinal canal (2). Banerji and Millar (3) state that the presenting features of the anomaly in adults are variable and may be deceptive, with the diagnosis only being made after radiologic investigation. The prognosis in such patients is good with conservative therapy, but when objective neurologic deficits develop, surgical decompression to establish free-flow cerebrospinal fluid (CSF) from the fourth ventricle may be required (4).

The prevailing opinion is that the herniation is secondary to congenital hydrocephalus (5). However, on the basis of several patients becoming symptomatic after placement of subarachnoid-peritoneal shunts, Welch et al. (6) postulated that it may be an acquired disorder. The common feature of both theories is that an increased gradient of CSF pressure develops between the brain and the spinal canal. A similar pressure differential, caused by CSF leakage, is also believed to account for the PDPH (7).

In this case, the presenting features were typical of PDPH. After conservative measures failed, an EBP was performed with initial success, supporting this diagnosis. Persistent PDPH is effectively treated by an EBP in approximately 95% of cases (8). Persistence or recurrence of a PDPH in obstetric patients neces-

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sitates reviewing alternative causes for headaches, such as cortical vein thrombosis (9,10). Prolonged headache with neurologic signs may indicate a subdural hematoma (11,12) requiring specific investigation. The finding of a Chiari I malformation on magnetic resonance imaging scan in this case led to the possibility that the headache was secondary to the Chiari I malformation. Whether the spinal puncture unmasked a preexisting malformation or created the anomaly is unknown. In either case, the Chiari I malformation should be considered in the differential diagnosis of persistent PDPH. Although there are no reported cases of the administration of spinal anesthesia in patients with a symptomatic Chiari I malformation, we believe that the choice of anesthesia should take into account the risk of increasing the CSF pressure gradient between the brain and the spinal canal when the diagnosis is known.

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Acute Respiratory Failure in a Patient With Acute Leukemia Undergoing Minor Surgery

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Advances in oncology therapy and interdisciplinary cooperation have improved the rate of remission and its duration in patients with leukemia. Interdisciplinary treatment includes the application of general anesthesia in patients (especially children) undergoing diagnostic procedures, implantation of long-term central venous catheters (Hickman, Broviac, Port-A-Cath), and surgical emergencies. We report a case of acute respiratory failure in a patient with acute leukemia and a white blood cell count $>100{,}000/mm^3$ (hyperleukocytosis).

Case Report

A 49-yr-old woman (67 kg, 166 cm) with acute myelogenous leukemia underwent general anesthesia for implantation of a Hickman catheter for continuation of chemotherapy. The patient had had slight chronic bronchitis that was treated with fenoterol. Preoperative lung function tests revealed only a slight reduction of the forced expiratory vital capacity in the first second (80% of predicted). Induction chemotherapy should have followed a schedule of thioguanine, cytosine arabinoside, and daunorubicin. Because of a high leukocyte count (white blood cell count before therapy of $279{,}000/mm^3$), a prephase of chemotherapy with low-dose continuously infused cytosine arabinoside ($50 mg/m^2$ daily) preceded implantation of the Hickman catheter by 3 days. This slight cytoreductive regime was completed with allopurinol, potassium hydrogencitrate, and controlled hydration to prevent tumor lysis syndrome. Leukopheresis was canceled because of low platelet and red blood cell count. Norfloxacin and amphotericin B solution were administered orally for prophylactic gut decontamination. Because of fever of unknown origin, empiric antibiotic treatment (ampicillin, ceftazidine, penicillin) was performed.

A chest radiograph and electrocardiogram 2 days before the intervention showed no abnormal findings. Routine laboratory findings included a white blood cell count of $234{,}000/mm^3$, hemoglobin 7.8 g/dL, platelet count $68{,}000/mm^3$, and prothrombin time 65% of control. Serum sodium and potassium and liver and kidney tests were within the normal range.

The patient was completely conscious and complained of slight dyspnea and moderate expectoration. Physical examination showed normal heart and lung status. Heart rate was approximately 110 beats/min, and arterial blood pressure was 140/80 mm Hg. Body temperature of 38.5°C was believed to be due to the tumor. The patient insisted on general anesthesia and therefore fasted overnight.

Anesthesia was induced with thiopental (400 mg IV), vecuronium (6 mg IV), and inhaled enflurane. The trachea was intubated, and anesthesia was maintained with enflurane, N_2O in O_2, and fentanyl (0.075 mg IV). Ventilation was controlled to maintain normocarbia. Oxygen saturation was 97%, and approximately 700 mL of lactated Ringer's solution was administered.

When surgery was completed, approximately 60 min after induction of anesthesia, the trachea was extubated. The patient showed spontaneous ventilation of 8.5 L/min at a rate of 16 breaths/min. She was orientated and complained of dyspnea, with an arterial O_2 saturation of 83% (on room air) measured by pulse oximetry. Application of O_2 via face mask (6 L/min) led to an arterial O_2 saturation of 91%. On auscultation, the lungs were clear. Arterial blood gas analysis showed Pao_2 54 mm Hg, $Paco_2$ 38.1 mm Hg, arterial pHa 7.40, and a calculated arterial O_2 saturation 87%. A chest radiograph (Figure 1) revealed an interstitial/alveolar pulmonary edema and a normal heart.

The trachea was reintubated, and controlled mechanical ventilation was established with a positive end-expiratory pressure of 8 cm H_2O. Blood gas analysis taken from an arterial catheter showed Pao_2 values between 160 and 250 mm Hg, with a fraction of inspired O_2 of 0.98. Pulse oximetry measured 99% arterial O_2 saturation. Serum calcium, potassium, and phosphorus were normal. Central venous pressure obtained through the Hickman catheter was approximately 4–6 mm Hg. An urethral catheter was inserted.

The patient was then transferred to the intensive care unit. Her status improved after mechanical ventilation and high-dose corticosteroid therapy. Her electrocardiogram was normal. Microbiologic specimens were negative. The cytoreductive prephase chemotherapy was continued, and the trachea was extubated on the third day postoperatively. Thioguanine, cytosine arabinoside, and daunorubicin therapy was then started. On the fifth day postoperatively, the

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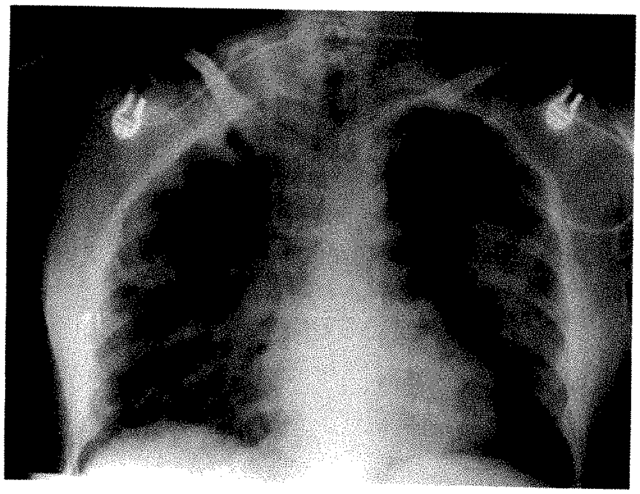

Figure 1. Anteroposterior radiograph of the chest obtained with portable apparatus in the supine position, taken in the immediate postoperative phase, revealing pulmonary edema of interstitial and alveolar pattern. The heart is of normal size, and a Hickman catheter is placed through the right internal jugular vein.

patient was admitted to the hematology ward. Two months later, she was discharged from hospital in complete remission.

Discussion

Because the patient had no history of cardiac disease, a normal electrocardiogram, central venous pressure of 4–6 mm Hg, and pulmonary edema with an interstitial/alveolar pattern, we concluded that she had developed a noncardiogenic pulmonary edema. Because aspiration of gastric contents and excessive intervascular volume could also be excluded, some particular features of leukemia and its therapy had to be considered to explain the acute respiratory failure. Acute dyspnea can be induced by the leukostasis syndrome as a symptom of the tumor lysis syndrome, or as a side effect of cytotoxic drugs.

Leukostasis syndrome describes the acute onset of pulmonary failure and, often, neurologic deficits in patients with hyperleukocytosis (1). Because leukocytes are less deformable than red blood cells, and blast cells are less deformable than mature cells, microvascular blood flow can be seriously affected (2,3). Moreover, the diameter of leukemic blast cells exceeds the internal diameter of capillaries and small vessels, leading to a mechanical obstruction of vessels by leukemic cells (1).

Activated by complement, leukocytes are capable of aggregating and marginating (i.e., sticking to the endothelium) (4,5), leading to parenchymal damage (1) by an exaggerated leukocytic oxygen consumption and the release of toxic respiratory "burst" products by the leukocytes (e.g., superoxide and proteases [elastase, collagenase]). Histologically, leukocyte thrombus, vessel occlusions, infiltration of the perivascular tissue, and parenchymal bleeding could be found (6).

The frequency of the syndrome is determined by the size, maturity, and number of leukocytes, so that approximately 15% of patients with chronic myelogenous leukemia, and only approximately 1% of those with chronic lymphocytic leukemia, develop leukostasis syndrome (7). This syndrome appears in the form of acute dyspnea and is often accompanied by confusion or disorientation and focal deficits due to cerebral perfusion impairment. Tinnitus, hearing loss, digital necrosis, priapism, retinal hemorrhage, and retinal vein distention sometimes occur (8). Neither hematocrit nor plasma viscosity is a predictor of leukostasis syndrome. Hematocrit does not change in these patients, because the increase in leukocyte count is compensated by a decrease in erythrocyte count, and plasma viscosity is not altered (3).

A typical sign for hyperleukocytosis is an alteration in arterial blood gas analysis. Chillar et al. (9) demonstrated in an in vitro study that Pa_{O_2} is significantly reduced within 30 s owing to exaggerated leukocytic oxygen consumption. With regard to the time necessary for drawing, cooling, and rewarming of the samples, cooling on ice can only prevent subsequent oxygen consumption during transport. Moreover, Loke and Duffy (10) showed a difference between the arterial oxygen saturation calculated from arterial blood gas analysis and that obtained by ear oximetry in patients with hyperleukocytosis. The authors observed a difference of 8% arterial oxygen saturation before cytoreductive therapy, which decreased to 2% after therapy. Thus, arterial blood gas analysis in patients with hyperleukocytosis is of questionable value, and the use of ear oximetry is recommended.

Leukostasis syndrome can be triggered by the application of red packed cells (11), deteriorating viscosity, or by surgery through complement activation (4). Leukostasis syndrome must be treated by cytoreduction via leukapheresis or cytotoxic drugs.

Patients with a large tumor cell mass (i.e., hyperleukocytosis) can develop tumor lysis syndrome in the first 2 days of chemotherapy (12). Lysis of a large number of tumor cells leads to hyperphosphatemia, hyperkalemia, hyperuricemia, and hypocalcemia. This syndrome is complicated by the precipitation of uric acid, xanthine, and phosphate in the renal tubules. This can impair renal excretory function, which in turn can lead to further elevation of these metabolites and even result in acute renal failure (3,12). In some cases of tumor lysis syndrome, acute respiratory failure occurs, induced by metabolites and cytolytic enzymes released from necrotic leukemic cells (1). Chest radiographs show a noncardiogenic pulmonary edema (1). Therapy requires, on the one hand, diuresis of $>3.0\ \mathrm{L{\cdot}m^{-2}{\cdot}24\ h^{-1}}$ to support renal function and, on the other, a negative fluid balance to treat pulmonary edema. Mechanical ventilation may be necessary, and high-dose corticosteroid therapy has been reported to be helpful (12).

Several chemotherapeutic drugs are responsible for acute or chronic respiratory failure. The only cytotoxic drug that was administered in our patient was cytosine arabinoside, which can cause a noncardiogenic pulmonary edema. This edema appears within the first 8 days of therapy and has a rapid onset within 1 or 2 h (13,14). This side effect was observed during cytosine arabinoside monotherapy of 300 $\mathrm{mg/m^2}$ to 1 $\mathrm{g/m^2}$ and more (13) and during therapy with low-dose cytosine arabinoside (100 $\mathrm{mg/m^2}$) in combination with other drugs (lomostine and daunorubicin) in up to 20% of treated patients (14). How the edema is initiated is not known, and no causal therapy has yet been established. Symptomatic therapy with oxygen applied via face mask, mechanical ventilation in severe cases, and high-dose corticosteroid therapy have been recommended (13).

In our patient, the discrepancy between the photometrically measured arterial oxygen saturation and that obtained by ear oximetry, the classification of a FAB M4/5 leukemia with hyperleukocytosis, the onset and development of dyspnea, the response to cell reduction, and the lack of tumor lysis signs (hyperphosphatemia, hyperkalemia, hyperuricemia, and hypocalcemia) led us to conclude that the patient had leukostasis syndrome that was associated with a noncardiogenic pulmonary edema.

Because of these particular features of leukemia and leukemia therapy, we conclude that the first days of chemotherapeutic therapy and hyperleukocytosis should be considered relative contraindications for general anesthesia and surgery. Anesthesiologists and surgeons who are responsible for the emergency care of these patients should be aware of the possible development of acute respiratory failure.

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Change of Ectopic Supraventricular Tachycardia to Sinus Rhythm During Administration of Propofol

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Paroxysmal supraventricular tachycardia is one of the most common dysrhythmias in infants and children. It is caused by altered normal automaticity of the sinus node or by abnormal automaticity of atrial cell compounds other than those responsible for normal pacemaker function (1,2). Perioperative provocation of such paroxysms by surgical stress or by anesthetic drugs should be avoided because persistent tachycardia may lead to congestive heart failure. Propofol anesthesia was administered to a child who had severe supraventricular tachycardia with paroxysms since birth. The child had been under close cardiologic monitoring, demonstrating that periods of regular sinus rhythm had been brief and extremely rare. Repetitive administration of propofol was associated with conversion to sinus rhythm, which remained stable for the entire surgical procedure.

Case Report

A 3.5-yr-old, 15-kg boy was scheduled for adenoidectomy and tympanic membrane incision because of recurrent otitis media. Such an infection had previously caused pneumococcus sepsis. The child suffered from supraventricular tachycardia based on ectopic monofocal atrial automaticity, suggesting a chronic ectopic atrial tachycardia (3). The surface electrocardiogram (ECG) showed narrow complex supraventricular tachycardia with marked changes in P-wave morphology during tachycardic episodes. The dysrhythmia had been diagnosed previously in utero and had to be treated with methyl-digoxin and verapamil. A therapeutic trial with propafenon and sotalol had been ineffective. Symptoms consisted of daily paroxysmal tachycardic episodes lasting 1–2 h, with heart rates of 200–250 beats/min. His prevailing "normal" heart rate was found to vary between 140 and 175 beats/min (ECG: ectopic atrial pacemaker) with brief periods at 75 beats/min (ECG: sinus rhythm with normal P-wave morphology). Paroxysms lasting longer than 60 min had previously caused clinical signs of congestive heart failure. The boy had therefore been under ECG monitoring at home. Although the tachycardic paroxysms occurred predominantly in the morning, no additional correlation with either physical activity or excitement or anxiety could be observed. No detailed invasive electrophysiologic procedures for focus localization had been performed, and the boy was scheduled for subsequent presentation in a cardiosurgical department to consider surgical excision of the ectopic focus.

On hospital admission, he was otherwise healthy and in good condition. In view of this, it was decided to dispense with a preoperative assessment with regard to left ventricular function. All laboratory findings were normal and serum potassium was 4.7 mmol/L. He was premedicated with a rectal instillation of 15 mg of midazolam, and he had received his regular oral morning dose of 40 mg of verapamil and one of his two daily doses of 0.05 mg of methyl-digoxin.

In the operating room, he appeared sedated and cooperative. A standard ECG lead II showed his heart rate to be 165 beats/min, arterial pressure 95/60 mm Hg, Sa_{O_2} 98% (pulse oximeter, Ohmeda, Biox 3700e). After well-tolerated preoxygenation, the child was anesthetized by injections of 2.7 mg/kg of propofol and 0.35 mg/kg of nalbuphine. On laryngoscopy, the glottis was wide open, and the trachea was intubated without using succinylcholine; neither bucking nor an increase in heart rate (still 165 beats/min) nor blood pressure occurred during intubation. An additional 20 mg of propofol was injected after intubation.

A few seconds later, his heart rate converted to a normal sinus rhythm at 75 beats/min (Figure 1). Anesthesia was maintained with repetitive injections of 10–20-mg doses of propofol approximately every 10 min while the boy's lungs were ventilated with an inspired fraction of O_2 of 0.3 and an inspired fraction of N_2O of 0.7. The surgical procedure was uneventful, and the child's sinus rhythm varied between 75 and 110 beats/min with an apparently normal P wave and was never interrupted by ectopic atrial or ectopic ventricular beats. Thirty-five minutes after tracheal extubation, his heart rate suddenly increased to 215 beats/min (ECG: ectopic atrial pacemaker) and did not return to the intraoperatively observed normal sinus rhythm (Figure 1). On arrival in the recovery room he was awake and cooperative, his heart rate subsequently declined to 160 beats/min, and his ECG was not different from that seen preoperatively. The child was discharged from the hospital in good condition,

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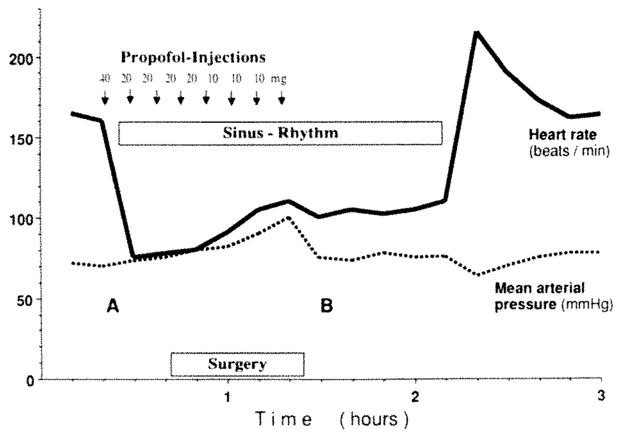

Figure 1. Diagram of heart rate and mean arterial blood pressure before, during, and after propofol anesthesia. On induction (**A**), supraventricular tachycardia converted to sinus rhythm, which converted back to supraventricular tachycardia 25 min after tracheal extubation (**B**).

and his dysrhythmias were not different from those observed before admittance.

Discussion

When considering all supraventricular tachycardias, the incidence of automatic atrial tachycardia is approximately 10% in children (4). Depending on the site of automaticity, these tachycardias can be subcategorized as inappropriate sinus tachycardia or chronic ectopic atrial tachycardia. The changing P-wave morphology suggests that our patient most likely had chronic ectopic atrial tachycardia (3). Paroxysmal tachycardia is characterized by sudden increases in heart rate to up to 250 beats/min. They may occur several times per day and may last from a few minutes up to 1 h, rarely longer (1).

The mechanisms thought to be responsible for these arrhythmias are disturbance of ionic membrane potentials, leading to an altered automaticity, extra sinoatrial focus sites, or AV node reentrant tachycardia (2,3). Among the external mechanisms triggering such supraventricular tachycardias are stress, drugs, ischemia, organ system disease, or electrolyte imbalance (2). Congestive heart failure and pulmonary edema may occur if the duration or the extent of the increase in heart rate decreases ventricular performance or ventricular filling, respectively. In addition, sustained automatic atrial tachycardia may lead to tachycardia-induced cardiomyopathy. Therefore, any surgical trigger stimulus should be suppressed, a concern of the anesthesiologist when choosing the anesthetic technique (5,6).

The rapidly acting hypnotic agent propofol (2,6-diisopropylphenol) has a short duration of action and is suitable for both induction and maintenance of anesthesia, either by continuous or by intermittent intravenous application (7).

Administration of propofol was found to have minimal effects on heart rate and rhythm, with even a tendency to lower heart rate (7). Propofol anesthesia is associated with a resetting of the tachycardiogenic baroreceptor reflex such that heart rate remains stable despite the drug's dose-related property to lower blood pressure (8). The comparably small sympathetic hemodynamic responses to endotracheal intubation during propofol induction, especially in combination with a narcotic agent (9), determined our choice of drugs. It seems unlikely that the observed change from supraventricular tachycardia to sinus rhythm in our patient was caused by nalbuphine because it has been found to leave myocardial function unaltered (10). We are unaware that nitrous oxide may affect myocardial conduction or sinus node automaticity.

Propofol, however, suppresses pacemaker automaticity and causes slowing of atrial conduction times in atrial preparations of rabbits and guinea pigs. This action of propofol was similar to the action of a local anesthetic. From another study in dogs it was concluded that the decreased activity of the sinus node after administration of propofol resembled an anion antagonistlike action, such as seen with alinidine (11).

In search of propofol's molecular site of action, a voltage-clamp study in human cell preparations found propofol to significantly prolong action potential-associated sodium channel conductance (12). Even though clinical relevance of such experimental findings remains to be proved, these results suggest a possible mechanism by which propofol may have converted tachycardic ectopic atrial pacemaker activity to sinus rhythm in our patient.

We cannot rule out that a decrease in sympathetic tone or an increase in vagal activity as a mere result of inducing general anesthesia may have contributed to the conversion to normal sinus rhythm. However, the observation that previous general anesthesia with halothane/nitrous oxide, which had been administered to our patient 3 yr earlier, left his ectopic supraventricular tachycardia almost unaltered suggests that the beneficial action of propofol was not simply caused by a nonspecific effect on the autonomic nervous system.

If propofol does possess a protective action against abnormal myocardial automaticity, further studies are needed to compare propofol with volatile anesthetics that may have both dysrhythmic and antidysrhythmic actions (2).

In summary, we report conversion of prevalent supraventricular tachycardia to normal sinus rhythm in a patient receiving propofol anesthesia. Previous administration of a volatile anesthetic to the child had not resulted in such normalization of the heart rate. Our observation indicates that propofol may be an appropriate anesthetic drug for patients with supraventricular tachycardia.

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Epidural Anesthesia in a Parturient Patient With Congenital Absence of the Inferior Vena Cava

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The congenital absence of the inferior vena cava (IVC) is uncommon (1,2). In these persons, venous drainage from structures below the diaphragm is diverted to collateral channels, including the azygous system, vertebral vessels (3), and superficial vessels in the abdominal wall (4). Although anomalous IVC occurs in 0.6% of patients with heart disease (5) and 1.0% of patients undergoing cardiac catheterization (6), the incidence of absent IVC is unknown. Pregnancy may adversely affect vascular malformations, resulting in serious complications (7).

Formation of the IVC (8) coincides with organization of the heart (9,10), liver (1,10), spleen (11), and lung (12,13) and rotation of the bowel (1) and formation of the pleuropericardial membrane (14). Coexisting abnormalities influence management of patients with anomalous or absent IVC. Pulmonary anomalies, such as arteriovenous malformations and dysgenesis of the bronchi (13), may disrupt oxygenation during positive pressure ventilation. Circulatory changes in the vertebral column (15) may profoundly affect subarachnoid and epidural techniques of regional anesthesia. We report the use of epidural regional anesthesia in a parturient patient with congenital absence of the IVC.

Case Report

A 34-yr-old woman (72 kg, 160 cm) was admitted for elective induction of labor at 41-wk gestation. Her history included hospital admission 1 yr previously for ruptured esophageal varices. During an exploratory laparotomy under general anesthesia, multiple vascular abnormalities were found, including congenital absence of the IVC and left renal vein. Devascularization of the stomach, splenectomy, and cholecystectomy were performed. Hemoglobin oxygen desaturation complicated the anesthetic course, the cause of which was not clearly understood. Postoperative respiratory insufficiency and hypoxia required mechanical ventilation for several weeks, but eventually the patient stabilized. Additional medical history included vascular insufficiency of the lower extremities, left renal insufficiency, and mitral valve prolapse. Physical examination on current admission was remarkable for stasis ulcerations, venous congestion and severe edema of the lower extremities, and numerous dilated superficial abdominal vessels. Laboratory studies were all normal.

Lactated Ringer's solution was administered through a peripheral venous line, and labor was induced by administration of oxytocin. Arterial blood pressure was measured by noninvasive oscillometric blood pressure machine. The patient requested epidural analgesia. In the sitting position, numerous dilated superficial veins were noted in the posterior lumbar region. A 17-gauge Tuohy needle was introduced into an area of skin devoid of superficial vessels and, using air loss-of-resistance technique, gently advanced to the epidural space via midline approach. Sterile saline solution (10 mL) was injected and the epidural catheter advanced into the space with no resistance. The catheter was tested with 2% lidocaine (2 mL) with 1:200,000 epinephrine. The patient was monitored closely for evidence of intrathecal or intravascular injection over a 5-min period; 0.25% bupivacaine (5 mL) was then administered in fractionated doses. After good onset of analgesia to a T-10 level, a continuous epidural infusion of 0.0625% bupivacaine and fentanyl (2.7 μg/mL) was started at 10 mL/h while the patient was positioned with left pelvic tilt.

Labor progressed well for 2.5 h, when fetal bradycardia occurred and persisted despite increased left lateral position and administration of supplemental oxygen. Maternal vital signs remained normal. Fetal heart rate was improved by Trendelenburg's position and appeared stable in this position for 45 min. However, serial fetal scalp samples revealed deteriorating acid-base status. When bradycardia recurred, the decision was made to deliver by cesarean section.

After the placement of pulse oximetry and an electrocardiogram, 2% lidocaine (10 mL) with 1:400,000 epinephrine was incrementally administered. Intense analgesia to a T-2 level was obtained within 7 min and cesarean section was performed uneventfully, delivering a normal male infant. The placenta was normal. Estimated blood loss was 450 mL. The epidural catheter was easily removed. Conva-

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lescence was uneventful, and on the fifth postoperative day mother and baby were discharged.

Discussion

During her previous experience with general anesthesia, our patient had encountered complications that may have been related to coexisting anomalies. Pulmonary abnormalities in similar patients include pulmonary dysgenesis (13), consisting of multiple branched, redundant bronchi with bronchial atresia, and arteriovenous malformations (12). Resultant intrapulmonary shunting may worsen during pregnancy (16). Positive pressure ventilation may further impede oxygenation by increasing dead-space ventilation (17) and may promote the rupture of pulmonary vascular anomalies with life-threatening consequences (18). Although aspiration of blood or respiratory distress syndrome from multiple transfusions may have contributed to the prolonged hypoxia during her first general anesthesia, coexisting pulmonary abnormalities had not been excluded. Repeating general anesthesia was considered undesirable. Regional anesthesia imparted several advantages: it allowed spontaneous ventilation to continue during surgical delivery, may have limited intraoperative blood loss (19), and improved uteroplacental blood flow during labor (20).

Patients with anomalous IVC have an increased epidural venous blood flow (2) that may be enhanced during pregnancy. Compression of the azygous-hemiazygous vessels may promote epidural blood flow changes analogous to caval compression. In some patients, however, predominance of venous return through superficial abdominal vessels may result in minimal epidural changes.

Management of regional anesthesia in these patients should include testing the position of the catheter with epinephrine-containing solutions (21) and slow, fractionated delivery of anesthetic, because accidental venous cannulation is more likely (22). Positioning the epidural needle with loss-of-resistance to air avoids confusing the clinical indices of accidental dural puncture in the presence of abnormal vertebral anatomy (23). Lubricating the epidural space with saline solution may facilitate passage of the catheter and minimize the chance of vessel injury (24) and epidural hematoma formation (25,26). Smaller doses of anesthetic are needed, because the enlarged venous compartment limits the epidural space and enhances the spread of anesthetic (27). Highly lipid-soluble local anesthetics or additional epinephrine may also minimize systemic uptake (28).

In patients with significant clinical deterioration during pregnancy or coexisting cardiac abnormalities, invasive monitoring should be considered during labor. In those without compromise, however, noninvasive monitoring may be adequate, eliminating the risk of placing catheters into potentially anomalous vessels.

Alleviation of maternal hypotension and uteroplacental insufficiency by left lateral position (29,30) may be ineffective in these patients. Left lateral tilt had no significant impact on fetal heart rate decelerations in our case, but Trendelenburg's position improved the fetal condition without compromising the mother's vital signs.

This case demonstrates epidural regional anesthesia for labor and cesarean section in a patient with congenital absence of the IVC. Associated systemic abnormalities must be considered during the management of such patients, with particular attention to the increased blood flow in the epidural space and its implications.

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Glossopharyngeal Nerve Block for Carotid Sinus Syndrome

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Carotid sinus syndrome (CSS) is caused by hyperactivity of the carotid sinus reflex and is categorized as type 1, cardioinhibitory; type 2, vasodepressor; and type 3, mixed. Syncope and dizziness are common symptoms (1,2). Several therapeutic measures have been recommended for CSS, including cardiac pacemaker implantation, radiation, surgical denervation of the carotid sinus, and various drug therapies. However, an optimal treatment for CSS has not yet been established (3). We report a case of mixed-type CSS secondary to a malignant lymphoma of the pharynx, the symptoms of which were completely ameliorated by a glossopharyngeal nerve block.

Case Report

A 76-yr-old man with a left cervical mass was admitted to the coronary care unit with repetitive syncopal episodes. During this admission, he developed a sinus bradycardia of 36 beats/min, followed by severe hypotension (56/36 mm Hg). Left carotid sinus massage reliably reproduced his symptoms. Computed tomography of the neck and biopsy of the cervical mass revealed a malignant lymphoma of the pharynx involving the left carotid sinus. We diagnosed a mixed-type CSS due to a malignant lymphoma of the pharynx. His symptoms were refractory to temporary cardiac pacing and combined drug therapy with atropine sulfate (1.5 mg/day), midodrine hydrochloride (6 mg/day), and fludrocortisone acetate (1 mg/day). A left selective glossopharyngeal nerve block was performed to reduce the afferent impulse from the left carotid sinus. A 5-cm insulated needle was inserted at the midpoint between the angle of the mandible and the tip of the mastoid process. The needle was advanced to the styloid process and then drawn back to the skin and reinserted anterior to the styloid process with intermittent electrical stimulation and continuous aspiration through the needle. The needle was advanced until the patient felt a vague, oppressive sensation radiating to his left external ear canal and epipharynx. No evidence of cranial nerve stimulation was noted, and no blood was aspirated during insertion of the needle. Three milliliters of 1% mepivacaine was injected through the needle. Five minutes later, the left and right carotid sinus reflexes were compared with each other. Left carotid sinus massage induced less bradycardia than that on the right (Figure 1). Correct needle position was confirmed by plain roentgenography of the basal skull and computed tomography of the neck (Figure 2). The glossopharyngeal nerve block was effective until the anesthetic action of the injected mepivacaine disappeared. Two days later, 1 mL of pure ethanol was injected to obliterate the left glossopharyngeal nerve. Since then, the patient has had a complete remission of symptoms.

Discussion

Cardiac pacemaker implantation is the preferred treatment for type 1 CSS. However, it is less effective for types 2 and 3 CSS because the restoration of a normal heart rate does not result in normotension (3). In these patients, treatment options include the administration of vasoconstrictive agents or procedures to reduce the afferent outflow from the carotid sinus. A permanent glossopharyngeal nerve block may relieve a patient with a mixed-type CSS from recurrent syncope and circulatory collapse.

Selective glossopharyngeal nerve block is a relatively difficult procedure and is associated with a number of potential complications (4,5). Nerve block may be more difficult in a patient with a neck tumor, owing to displacement of the glossopharyngeal nerve. To avoid injury to nearby nerves and vessels, we used an insulated needle with intermittent electrical stimulation and continuous aspiration. Correct needle position was determined by the patient's reporting a vague sensation radiating to the area supplied by the glossopharyngeal nerve. A decreased heart rate response to the carotid sinus massage compared with that on the unblocked side after infiltration of a local anesthetic provided further evidence of correct placement. Finally, the position of the needle was confirmed by plain roentgenography of the basal skull and computed tomography of the neck.

In conclusion, we report the effectiveness of a

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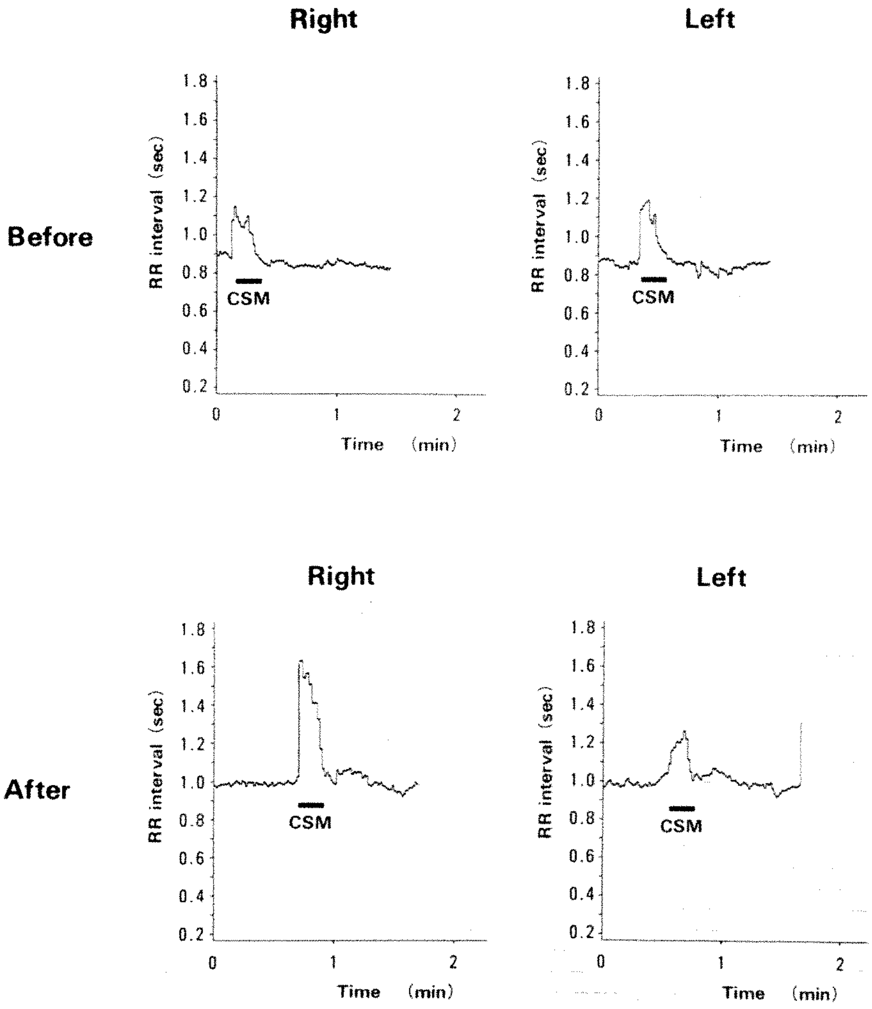

Figure 1. R-R interval trendgram during carotid sinus massage (CSM). In contrast to before the nerve block (*upper panels*), a smaller response to CSM on the left compared with that on the right is noted after the nerve was blocked (*lower panels*).

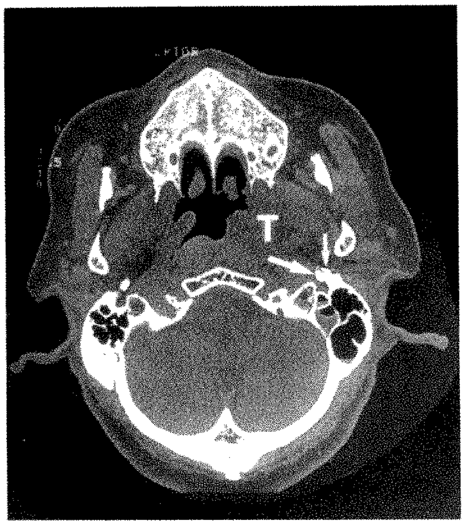

Figure 2. Computed tomography scan of the neck showing malignant lymphoma of the left pharynx (*T*); *large arrow*, the styloid process; *small arrow*, tip of the insulated needle.

glossopharyngeal nerve block in a patient with mixed-type CSS secondary to a malignant lymphoma of the pharynx. Glossopharyngeal nerve block is an alternative therapy in patients with CSS who are refractory to drug and pacemaker therapy.

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Dorsal Primary Ramus Nerve Block for Treatment of Low Back Pain After Epidural Analgesia

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New low back pain due to intrathecal or epidural injection is a puzzling and often frustrating problem for the anesthesiologist. This is especially confounding when the back pain is associated with radicular symptoms indicating, at least to the patient, that the injection may have resulted in nerve damage. Most anesthesiologists attribute postepidural back pain to local trauma and reassure patients that this will resolve in a few days. Other causes of back pain after epidural or spinal anesthesia might include needle puncture of an intervertebral disk or flattening of the normal lumbar lordosis owing to muscle relaxation, thus allowing stretching of the joint capsules and ligaments beyond their physiologic range (1). However, the problem becomes more complicated when the back pain either persists or radicular symptoms become evident.

Back pain after intraspinal injection may be similar to that in facet syndrome. Pain is of an aching quality in the lower lumbar region, with or without radiation to the buttock or posterior thigh. Tenderness is elicited with palpation over the paraspinal muscles or facet joints, or both (2). In our experience, the so-called facet syndrome responds well to blockade of the dorsal primary ramus, which innervates the facet joint. Dorsal primary ramus nerve block achieves the same goal as facet joint injection but with more complete analgesia of the posterior midline structures. In this report, we discuss two patients who presented to the Pain Management Center at the University of California, San Francisco, with prolonged midline back pain after epidural anesthesia. Their pain was completely relieved with dorsal primary ramus nerve blocks at the levels indicated by local back pain symptoms. This is the first report of such treatment for postepidural back pain.

Case Reports

Case 1

A 36-yr-old woman (58 kg) had a peroneal nerve injury with foot drop after a total hip replacement, under general anesthesia, for degenerative arthritis. In the immediate postoperative period, she noted pain in the foot; her foot was also cool and moist. One month later, she was referred to the Pain Management Center, where a diagnosis of reflex sympathetic dystrophy was made. Of note, the patient did not complain of back pain on her initial presentation to the Pain Management Center. After a lumbar sympathetic block with a single bolus injection of 0.5% bupivacaine (6 mL), the patient expressed moderate-to-good pain relief, and increased skin temperature and blood flow were noted; however, analgesia lasted for only 2 days. Administration of a second sympathetic block (0.25% bupivacaine, 10 mL) produced adequate sympathectomy but no pain relief.

Considering the failed sympathetic block and the probability of a primarily neuropathic pain syndrome, we elected to pursue a course of epidural analgesia. An initial, single bolus epidural injection of 0.125% bupivacaine (10 mL) with fentanyl (50 μg) at the L3-4 level resulted in good pain relief. Subsequently, the patient was admitted to the hospital for a continuous epidural infusion of 0.0625% bupivacaine (12 mL/h) and fentanyl (50 μg/h) via a catheter placed at the L2-3 level. The patient experienced good pain relief during the epidural infusion; however, the patient's pain recurred whenever the infusion rate was reduced. Because of this breakthrough pain, it was elected to continue the patient's treatment with epidural infusion, at initial rates, as an outpatient. This was facilitated by the home therapy service, which arranged a home infusion pump and follow-up management. Before discharge, a third epidural puncture (L3-4) for catheter replacement was performed. An inadvertent dural puncture at this time necessitated a fourth epidural injection (L2-3) for blood patch.

We elected to terminate treatment with epidural infusion and manage the patient's pain medically with a regimen of tricyclic antidepressants and prazosin. However, she developed persistent midline low back pain at the L3-4 level, with radiation to the lateral right leg. In addition, examination revealed tender right paraspinous muscle spasm but no neurologic deficits other than the foot drop, which preexisted the epidural punctures. We elected to

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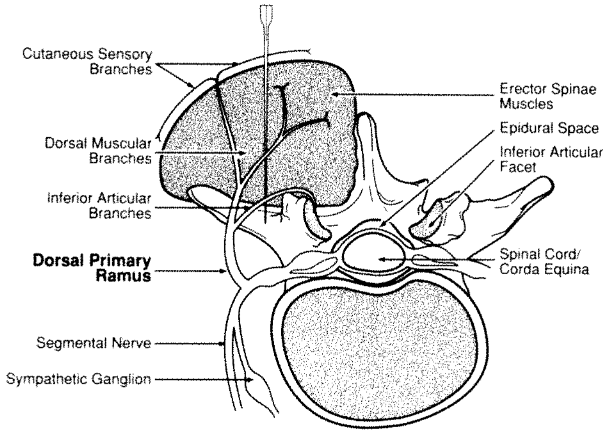

Figure 1. Segmental innervation of the dorsal spinal structures. Posterior elements are innervated by the dorsal primary ramus. The needle rests at the junction of the transverse process (medial one-third) with the dorsal lumbar process of the vertebral body, as in administration of a dorsal primary ramus nerve block. (Adapted from Boas [Reference 2], page 200, with permission.)

treat the patient using dorsal primary ramus nerve blocks at the L3 and L4 levels.

Dorsal primary ramus nerve blocks were performed according to the technique described previously by Boas (2) (Figure 1). Twenty-two-gauge spinal needles were advanced under fluoroscopy to the junction of the transverse process with the dorsal lumbar process of the vertebral body bilaterally at the L3 and L4 levels. Two milliliters of 0.5% bupivacaine was injected at each of the four sites. Within 30 min, her back pain was completely relieved (pain score 6/10 before injection; 0/10 after injection) and has not recurred 12 mo later.

Case 2

A 36-yr-old woman (52 kg) complained of 1.5 yr of localized midline back pain after epidural analgesia (via a catheter placed at the L3-4 level) for vaginal delivery. Her pain was constant, midline, and without radiation. It was worse in the prone position, while flexing at the waist, or while carrying her child. Her back pain was refractory to physical therapy and a single intraligamentous steroid injection (L2-3 level) performed in the orthopedic clinic. Her physical examination was significant for a decrease in muscle strength in the right leg secondary to a childhood history of polio and local tenderness at the L2 and L3 interspace in the midline, as well as over the adjacent facet joints. She underwent bilateral L2 and L3 dorsal primary ramus nerve blocks (2) with 0.5% bupivacaine (2 mL per injection at each of four sites) with complete relief of her pain. Two months later, pain recurred, and she again underwent dorsal primary ramus nerve blocks, this time with a mixture of 0.5% bupivacaine (1.5 mL) and triamcinolone (15 mg) at each injection site. Steroid was added to the treatment regimen in an attempt to achieve longer lasting pain relief. Her pain was completely relieved and has not recurred approximately 22 mo later.

Discussion

Epidurally administered local anesthetics or narcotics, or both, are often used for treatment of various pain syndromes. When the epidural injection itself causes an additional persistent pain problem, frustration and disappointment can result. Although effective therapy for persistent back pain induced by intraspinal injection has not been described, our success in two patients with a dorsal primary ramus nerve block is encouraging.

That a dorsal primary ramus nerve block may be successful has some anatomic and scientific basis. As early as the mid-1930s, it was recognized that as much as 80% of back pain with sciatic radiation was due to referred pain and not direct nerve irritation (3). In 1933, Ghormley (4) used the term "facet syndrome" to describe the syndrome of back pain with sciatic radiation presumed secondary to disorders of the vertebral facet joint, not to direct nerve root compression. In 1985, Peng and colleagues (5) reported a reduction of prolonged backache after lumbar puncture from 3% to 0% using a field block technique to anesthetize posterior midline structures before intraspinal injection.

Posterior midline structures, including the facet joint, are richly innervated with somatic and autonomic nerves. Yet, despite the attention placed on the anatomy of dorsal structures in the performance of epidural and spinal anesthesia, many anesthesiologists may be unfamiliar with the innervation of these structures. In 1956, Stillwell (6) described the innervation of the vertebral column and associated structures in primates. His findings were confirmed in humans by Pedersen et al. (7). The posterior midline structures are innervated mainly by the dorsal primary ramus of each spinal segmental nerve. Rami communicantes connect spinal and sympathetic ganglia and allow autonomic fibers to refer to the dorsal primary ramus. Somatic axons from the dorsal primary ramus are similarly communicated back to the autonomic plexus that surrounds the vertebral artery. Branches from the dorsal primary ramus, carrying somatic and autonomic fibers, innervate the posterior longitudinal ligament, interspinous and flaval ligaments, sacrospinalis muscle, lumbodorsal fascia, and facet joints. Branches of the paravertebral plexus supply the anterior longitudinal ligament, dura mater, annulus fibrosis, periosteum, and bone (6–8) (Figure 1). Because axons from the segmental nerves enter the paravertebral plexus before distribution, there is some overlap of innervation. Also, facet joints receive dual innervation, with the inferior articular surface being innervated by the segmental nerve at its level and the superior articular surface being innervated by the segmental nerve one level cephalad (2). This may explain why the patient in case 2 experienced pain one level below her initial epidural injection.

The performance of a routine epidural anesthetic encroaches on many of the posterior midline structures. Ligaments are initially penetrated, periosteum may be contacted, and the dura may be encroached on during the passage of the epidural catheter. A misdirected needle can trespass on muscle, fascia, periosteum, dura, and even facet joints. Local trauma may be increased in the patient who requires multiple epidural anesthetics or multiple attempts at localizing the epidural space. Although direct trauma may cause localized pain, persistent or radiating pain requires further explanation.

In 1939, Kellgren (9) demonstrated that local trauma caused by injection of hypertonic saline into interspinous ligament resulted in patterns of local and referred pain in a segmental distribution. Similar referral patterns were found after injection of muscle, fascia, tendons, and periosteum. Basically, local pain caused by injection of hypertonic saline was referred to other areas with the same spinal segmental innervation (9,10).

Persistent or radiating back pain after epidural anesthesia can be explained on the basis of the innervation of dorsal structures as well as knowledge of pain referral patterns. The rich innervation of posterior structures with somatic and autonomic fibers can explain pain as a result of trauma to tissues innervated by the posterior segmental nerves. Pain is referred, as proposed by Kellgren (9), to more distal areas innervated by the same segmental nerve and maintained either sympathetically or somatically owing to muscle spasm.

In summary, we present two cases of persistent back pain after epidural analgesia successfully treated with dorsal primary ramus nerve blocks. To our knowledge, this is the first report of this therapy for back pain after intraspinal injection. We propose that this back pain is caused by local trauma to nerves innervating structures trespassed during the injection. It remains to be determined whether repeated injections or multiple attempts to identify the "difficult" epidural space may more commonly precipitate this pain. Pain is referred in a spinal segmental pattern. Pain is relieved with a dorsal primary ramus nerve block by interrupting the sympathetic or somatic cycle that maintains the pain. We suggest that early consideration be given to dorsal primary ramus nerve block as a potential treatment for persistent back pain after intraspinal anesthesia.

The editorial assistance of Winifred Von Ehrenburg in the review and preparation of this manuscript is greatly appreciated.

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Continuous Stellate Ganglion Blockade for Reflex Sympathetic Dystrophy

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Reflex sympathetic dystrophy (RSD) is a syndrome comprising burning pain, hyperalgesia, and allodynia alone or in combination with vasomotor and dystrophic changes and may be related to peripheral nerve injury (1). Sympathetic blockades are often performed to relieve the symptoms of RSD. Both central sympathetic ganglion blockade using a local anesthetic and Bier block with guanethidine or reserpine have been employed with varying success (2). Such treatments are often performed as a series of sympathetic nerve blocks. The following case describes a new method for the continuous blockade of the cervical sympathetic ganglia in a patient resistant to other forms of treatment.

Case Report

A 31-yr-old woman presented with several months' history of piercing pain in her right shoulder, with occasional radiation to the right hand. Symptoms of RSD were present in the right hand in the form of color change, hyperhidrosis, and allodynia. A diagnosis of brachial plexus neuritis after minor trauma 2 yr earlier had been made based on the clinical picture and an electromyographic examination that showed evidence of denervation plus delayed polyphasic potentials. Previous therapy with simple analgesics, oral steroids, massage, trigger point injections, and transcutaneous nerve stimulation plus a series of Bier blocks with guanethidine had failed to relieve the shoulder pain or reduce the sympathetic overactivity. The patient presented with severe pain, a score of 9 using a visual analogue scale (VAS 0–10), and she had about 10 episodes of sympathetic overactivity daily. She was taking no medication.

A sympathetic blockade of the stellate ganglion provided pain relief, after which it was decided to perform a continuous blockade of the ganglion. After locating the transverse process of C7 using an intravenous cannula (gauge 17 Venflon), an epidural catheter was threaded into position on the suface of the same transverse process. The catheter was sutured to the skin and covered with a sterile translucent plaster. A test dose of 1% lidocaine (8 mL) resulted in Horner's syndrome, and the catheter was then attached to a transportable infusion pump with a 100-mL cassette (Figure 1). A mixture of 0.25% bupivicaine with 4 mg morphine/100 mL was infused at a rate of 6–8 mL/h. During this treatment, the patient became symptom free. At the end of 7 days, the treatment was stopped, and the patient was asked to score shoulder pain and the number of episodes of sympathetic overactivity. Pain score (VAS) had decreased from 9 to 5 and sympathetic overactivity from 10 to 2 episodes daily.

During the following weeks, a series of four continuous blockades using a new catheter and each lasting 3 days was performed, during which the patient was symptom free and after which the pain score (VAS) and sympathetic episodes had been further reduced to 2 and 0, respectively. The improvement is still present several months later, although a tendency for relapse of the shoulder pain during exertion (e.g., badminton) is an irritation to the patient.

Discussion

Although the pathophysiology of RSD is poorly understood, it is well known that increased sympathetic activity reduces the threshold of nociceptors. The fact that many of the symptoms of RSD are relieved by sympathetic blockade is supportive of the theory that the pain in RSD is sympathetically maintained (3).

Single injection of the stellate ganglion has provided pain relief of longer duration than the action of the local anesthetic would suggest. In cases in which central sympathetic blockade provides relief of symptoms, it would seem logical to give a continuous blockade instead of single shots. This approach will result in a prolonged absence of sympathetic overactivity, at the same time reducing the input of painful afferent stimuli to the central nervous system, thus reversing the process of central hyperexcitability and increasing the likelihood of a return to a more normal discrimination of pain information (4).

Morphine was added to the infusion to maintain the maximal level of sensory analgesia (5). This morphine may in fact have had an effect on sensory perception via intrinsic local anesthetic properties (6)

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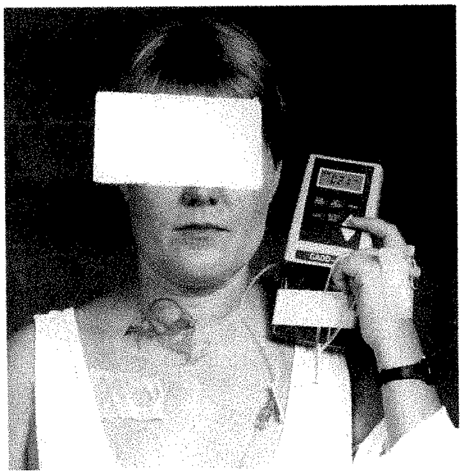

Figure 1. The patient with an epidural catheter connected to a portable infusion pump.

and on centrally placed morphine receptors via diffusion to the dorsal column of the spinal cord.

Although there is no anatomic space that can be located in the same way as the epidural space, an epidural catheter could be placed in close relation to the sympathetic ganglia on five successive occasions and a continuous sympathetic blockade achieved. There were no signs of toxicity to the local anesthetic, and infusion rates of the same order of magnitude are used to treat postoperative pain in our hospital.

The technique is thus an alternative to the established method consisting of a series of "single-shot" injections in RSD. The technique is only suitable for patients who can be admitted to the hospital for observation during the period of infusion.

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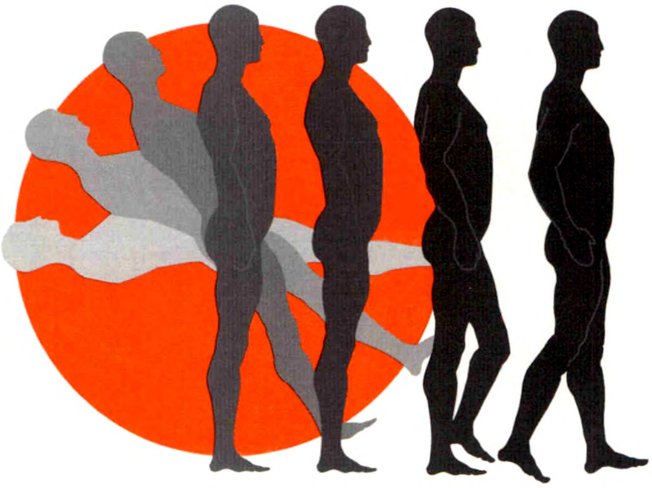

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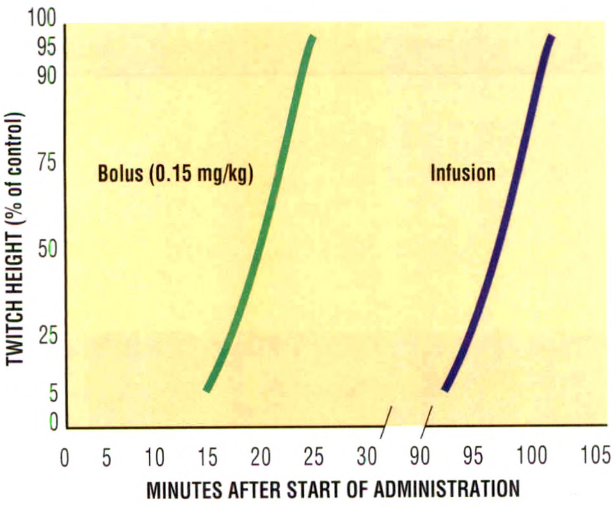


Adapted fom Savarese et al, p. 727.[1]

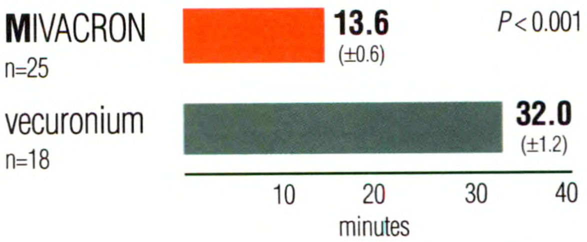
Noncumulative—minimal rate adjustments needed

Continuous infusion for up to 2.5 hours is not associated with tachyphylaxis or cumulative neuromuscular block in ASA Physical Status I-II patients (data for infusions > 2.5 hours are limited).

> "Steady-state levels of block may be produced rapidly with minimal adjustment of the infusion rate and a consistent rate of recovery occurs...."

Ali et al, p.544.[2]

Recovery time less than half that of vecuronium



Spontaneous recovery time (from discontinuation of infusion) 5-95%. Duration of continuous infusion for MIVACRON: 86.2 ± 5.6 minutes; for vecuronium: 96.8 ± 6.6 minutes.

Adapted fom Ali et al, p. 544.[2]

*from discontinuation of infusion

Important note: Patients homozygous for the atypical plasma cholinesterase gene (1 in 2500) are extremely sensitive to Mivacron. Mivacron should be used with great caution, if at all, in these patients.

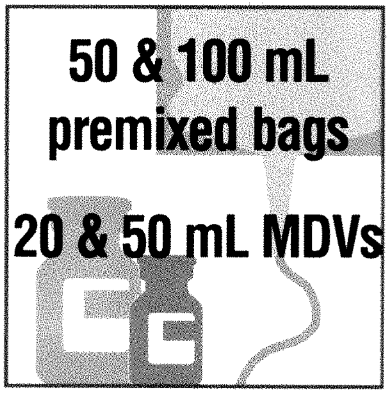
by Infusion

Minimal CV effects

During clinical trials with bolus dosing, the only adverse event with an incidence >1% was transient flushing (15%). No patient who received a 0.15 mg/kg bolus dose was treated for a decrease in blood pressure. Higher bolus doses (≥ 0.20 mg/kg, adults; ≥ 0.25 mg/kg, children) may be associated with transient decreases in MAP and increases in HR in some patients. During infusion, no significant CV effects were reported.

Individualization of infusion dosages

- Renal or hepatic disease
- Patients heterozygous for the atypical plasma cholinesterase gene



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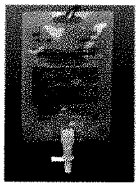
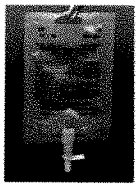


50 mL



100 mL

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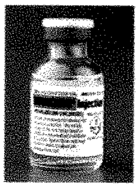
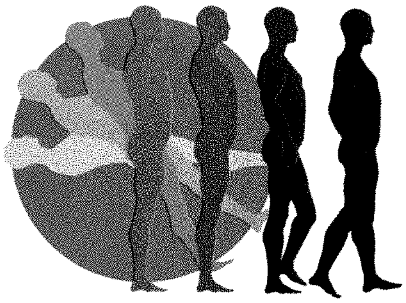


20 mL

50 mL



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Brief Summary

This drug should be administered only by adequately trained individuals familiar with its actions, characteristics, and hazards.

INDICATIONS AND USAGE: MIVACRON is a short-acting neuromuscular blocking agent indicated for inpatients and outpatients, as an adjunct to general anesthesia, to facilitate tracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

CONTRAINDICATIONS: MIVACRON is contraindicated in patients known to have an allergic hypersensitivity to mivacurium chloride or other benzylisoquinolinium agents, as manifested by reactions such as urticaria or severe respiratory distress or hypotension. Use of MIVACRON from multi-dose vials is contraindicated in patients with a known allergy to benzyl alcohol.

WARNINGS: MIVACRON SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH THE DRUG'S ACTIONS AND THE POSSIBLE COMPLICATIONS OF ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS PERSONNEL AND FACILITIES FOR RESUSCITATION AND LIFE SUPPORT (TRACHEAL INTUBATION, ARTIFICIAL VENTILATION, OXYGEN THERAPY), AND AN ANTAGONIST OF MIVACRON ARE IMMEDIATELY AVAILABLE. IT IS RECOMMENDED THAT A PERIPHERAL NERVE STIMULATOR BE USED TO MEASURE NEUROMUSCULAR FUNCTION DURING THE ADMINISTRATION OF MIVACRON IN ORDER TO MONITOR DRUG EFFECT, DETERMINE THE NEED FOR ADDITIONAL DRUG, AND CONFIRM RECOVERY FROM NEUROMUSCULAR BLOCK.

MIVACRON HAS NO KNOWN EFFECT ON CONSCIOUSNESS, PAIN THRESHOLD, OR CEREBRATION. TO AVOID DISTRESS TO THE PATIENT, NEUROMUSCULAR BLOCK SHOULD NOT BE INDUCED BEFORE UNCONSCIOUSNESS.

MIVACRON IS METABOLIZED BY PLASMA CHOLINESTERASE AND SHOULD BE USED WITH GREAT CAUTION, IF AT ALL, IN PATIENTS KNOWN TO BE OR SUSPECTED OF BEING HOMOZYGOUS FOR THE ATYPICAL PLASMA CHOLINESTERASE GENE.

MIVACRON Injection and MIVACRON Premixed Infusion are acidic (pH 3.5 to 5.0) and may not be compatible with alkaline solutions having a pH greater than 8.5 (*e.g.*, barbiturate solutions).

PRECAUTIONS:

General: Although MIVACRON (a mixture of three stereoisomers) is not a potent histamine releaser, the possibility of substantial histamine release must be considered. Release of histamine is related to the dose and speed of injection.

Caution should be exercised in administering MIVACRON to patients with clinically significant cardiovascular disease and patients with any history suggesting a greater sensitivity to the release of histamine or related mediators (*e.g.*, asthma). In such patients, the initial dose of MIVACRON should be 0.15 mg/kg or less, administered over 60 seconds; assurance of adequate hydration and careful monitoring of hemodynamic status are important (see **Hemodynamics** and **Individualization of Dosages** subsections of CLINICAL PHARMACOLOGY).

Obese patients may be more likely to experience clinically significant transient decreases in MAP than non-obese patients when the dose of MIVACRON is based on actual rather than ideal body weight. Therefore, in obese patients, the initial dose should be determined using the patient's ideal body weight (see **Hemodynamics** and **Individualization of Dosages** subsections of CLINICAL PHARMACOLOGY).

Recommended doses of MIVACRON have no clinically significant effects on heart rate; therefore, MIVACRON will not counteract the bradycardia produced by many anesthetic agents or by vagal stimulation.

Neuromuscular blocking agents may have a profound effect in patients with neuromuscular diseases (*e.g.*, myasthenia gravis and the myasthenic syndrome). In these and other conditions in which prolonged neuromuscular block is a possibility (*e.g.*, carcinomatosis), the use of a peripheral nerve stimulator and a dose of not more than 0.015–0.020 mg/kg MIVACRON is recommended to assess the level of neuromuscular block and to monitor dosage requirements (see **Individualization of Dosages** subsection of CLINICAL PHARMACOLOGY).

MIVACRON has not been studied in patients with burns. Resistance to nondepolarizing neuromuscular blocking agents may develop in patients with burns, depending upon the time elapsed since the injury and the size of the burn. Patients with burns may have reduced plasma cholinesterase activity which may offset this resistance (see **Individualization of Dosages** subsection of CLINICAL PHARMACOLOGY).

Acid-base and/or serum electrolyte abnormalities may potentiate or antagonize the action of neuromuscular blocking agents. The action of neuromuscular blocking agents may be enhanced by magnesium salts administered for the management of toxemia of pregnancy (see **Individualization of Dosages** subsection of CLINICAL PHARMACOLOGY).

No data are available to support the use of MIVACRON by intramuscular injection.

Renal and Hepatic Disease: The possibility of prolonged neuromuscular block must be considered when MIVACRON is used in patients with renal or hepatic disease (see **Pharmacokinetics** subsection of CLINICAL PHARMACOLOGY). Most patients with chronic hepatic disease such as hepatitis, liver abscess, and cirrhosis of the liver exhibit a marked reduction in plasma cholinesterase activity. Patients with acute or chronic renal disease may also show a reduction in plasma cholinesterase activity (see **Individualization of Dosages** subsection of CLINICAL PHARMACOLOGY).

Reduced Plasma Cholinesterase Activity: The possibility of prolonged neuromuscular block following administration of MIVACRON must be considered in patients with reduced plasma cholinesterase (pseudocholinesterase) activity.

Plasma cholinesterase activity may be diminished in the presence of genetic abnormalities of plasma cholinesterase (*e.g.*, patients heterozygous or homozygous for the atypical plasma cholinesterase gene), pregnancy, liver or kidney disease, malignant tumors, infections, burns, anemia, decompensated heart disease, peptic ulcer, or myxedema. Plasma cholinesterase activity may also be diminished by chronic administration of oral contraceptives, glucocorticoids, or certain monoamine oxidase inhibitors and by irreversible inhibitors of plasma cholinesterase (*e.g.*, organophosphate insecticides, echothiophate, and certain antineoplastic drugs).

MIVACRON has been used safely in patients heterozygous for the atypical plasma cholinesterase gene. At doses of 0.10 to 0.20 mg/kg MIVACRON, the clinically effective duration of action was 8 to 11 minutes longer in patients heterozygous for the atypical gene than in genotypically normal patients.

As with succinylcholine, patients homozygous for the atypical plasma cholinesterase gene (1 in 2500 patients) are extremely sensitive to the neuromuscular blocking effect of MIVACRON. In three such adult patients, a small dose of 0.03 mg/kg (approximately the ED_{10-20} in genotypically normal patients) produced complete neuromuscular block for 26 to 128 minutes. Once spontaneous recovery had begun, neuromuscular block in these patients was antagonized with conventional doses of neostigmine. One adult patient, who was homozygous for the atypical plasma cholinesterase gene, received a dose of 0.18 mg/kg MIVACRON and exhibited complete neuromuscular block for about 4 hours. Response to post-tetanic stimulation was present after 4 hours, all four responses to train-of-four stimulation were present after 6 hours, and the patient was extubated after 8 hours. Reversal was not attempted in this patient.

Malignant Hyperthermia (MH): In a study of MH-susceptible pigs, MIVACRON did not trigger MH. MIVACRON has not been studied in MH-susceptible patients. Because MH can develop in the absence of established triggering agents, the clinician should be prepared to recognize and treat MH in any patient undergoing general anesthesia

Long-Term Use in the Intensive Care Unit (ICU): No data are available on the long-term use of MIVACRON in patients undergoing mechanical ventilation in the ICU.

Drug Interactions: Although MIVACRON (a mixture of three stereoisomers) has been administered safely following succinylcholine-facilitated tracheal intubation, the interaction between the stereoisomers in MIVACRON and succinylcholine has not been systematically studied. Prior administration of succinylcholine can potentiate the neuromuscular blocking effects of nondepolarizing agents. Evidence of spontaneous recovery from succinylcholine should be observed before the administration of MIVACRON.

The use of MIVACRON before succinylcholine to attenuate some of the side effects of succinylcholine has not been studied.

There are no clinical data on the use of MIVACRON with other nondepolarizing neuromuscular blocking agents.

Isoflurane and enflurane (administered with nitrous oxide/oxygen to achieve 1.25 MAC) decrease the ED_{50} of MIVACRON by as much as 25% (see **Pharmacodynamics** and **Individualization of Dosages** subsections of CLINICAL PHARMACOLOGY). These agents may also prolong the clinically effective duration of action and decrease the average infusion requirement of MIVACRON by as much as 35% to 40%. A greater potentiation of the neuromuscular blocking effects of the stereoisomers in MIVACRON may be expected with higher concentrations of enflurane or isoflurane. Halothane has little or no effect on the ED_{50}, but may prolong the duration of action and decrease the average infusion requirement by as much as 20%.

Other drugs which may enhance the neuromuscular blocking action of nondepolarizing agents such as the stereoisomers in MIVACRON include certain antibiotics (*e.g.*, aminoglycosides, tetracyclines, bacitracin, polymyxins, lincomycin, clindamycin, colistin, and sodium colistimethate), magnesium salts, lithium, local anesthetics, procainamide, and quinidine. Drugs that may enhance the neuromuscular blocking effects of mivacurium by a reduction in plasma cholinesterase activity include chronic administration of oral contraceptives, glucocorticoids, or certain monoamine oxidase inhibitors and by irreversible inhibitors of plasma cholinesterase (see **Reduced Plasma Cholinesterase Activity** subsection of PRECAUTIONS).

Resistance to the neuromuscular blocking action of nondepolarizing neuromuscular blocking agents has been demonstrated in patients chronically administered phenytoin or carbamazepine. While the effects of chronic phenytoin or carbamazepine therapy on the action of the stereoisomers in MIVACRON are unknown, slightly shorter durations of neuromuscular block may be anticipated and infusion rate requirements may be higher.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis and fertility studies have not been performed. MIVACRON was evaluated in a battery of four short-term mutagenicity tests. It was non-mutagenic in the Ames Salmonella assay, the mouse lymphoma assay, the human lymphocyte assay, and the *in vivo* rat bone marrow cytogenetic assay.

Pregnancy: *Teratogenic Effects*: Pregnancy Category C. Teratology testing in nonventilated pregnant rats and mice treated subcutaneously with maximum subparalyzing doses of MIVACRON revealed no maternal or fetal toxicity or teratogenic effects. There are no adequate and well-controlled studies of MIVACRON in pregnant women. Because animal studies are not always predictive of human response, and the doses used were subparalyzing, MIVACRON should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: The use of MIVACRON during labor, vaginal delivery, or cesarean section has not been studied in humans and it is not known whether MIVACRON administered to the mother has effects on the fetus. Doses of 0.08 and 0.20 mg/kg MIVACRON given to female beagles undergoing cesarean section resulted in negligible levels of the stereoisomers in MIVACRON in umbilical vessel blood of neonates and no deleterious effects on the puppies.

Nursing Mothers: It is not known whether any of the stereoisomers of mivacurium are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised following administration of MIVACRON to a nursing woman.

Pediatric Use: MIVACRON has not been studied in children below the age of 2 years (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION for clinical experience and recommendations for use in children 2 to 12 years of age).

Geriatric Use: MIVACRON was safely administered during clinical trials to 64 elderly (≥65 years) patients, including 31 patients with significant cardiovascular disease (see **General** subsection of PRECAUTIONS). The duration of neuromuscular block may be slightly longer in elderly patients than in young adult patients (see CLINICAL PHARMACOLOGY).

ADVERSE REACTIONS:

Observed in Clinical Trials: MIVACRON (a mixture of three stereoisomers) was well tolerated during extensive clinical trials in inpatients and outpatients. Prolonged neuromuscular block, which is an important adverse experience associated with neuromuscular blocking agents as a class, was reported as an adverse experience in 3 of 2074 patients administered MIVACRON. The most commonly reported adverse experience following the administration of MIVACRON was transient, dose-dependent cutaneous flushing about the face, neck, and/or chest. Flushing was most frequently noted after the initial dose of MIVACRON and was reported in about 20% of adult patients who received the recommended dose of 0.15 mg/kg MIVACRON over 5 to 15 seconds. When present, flushing typically began within 1 to 2 minutes after the dose of MIVACRON and lasted for 3 to 5 minutes. Of 60 patients who experienced flushing after 0.15 mg/kg MIVACRON, one patient also experienced mild hypotension that was not treated, and one patient experienced moderate wheezing that was successfully treated.

Overall, hypotension was infrequently reported as an adverse experience in the clinical trials of MIVACRON. None of the 397 adults or 63 children who received recommended doses was treated for a decrease in blood pressure associated with the administration of MIVACRON. Above the recommended dosage range, 1% to 2% of healthy adults given ≥0.20 mg/kg over 5 to 15 seconds and 2% to 4% of cardiac surgery patients given ≥0.20 mg/kg over 60 seconds were treated for decreases in blood pressure associated with the administration of MIVACRON.

The following adverse experiences were reported in patients administered MIVACRON (all events judged by investigators during the clinical trials to have a possible causal relationship):

Incidence Greater Than 1% -

Cardiovascular:	Flushing (15%)

Incidence Less Than 1% -

Cardiovascular:	Hypotension, Tachycardia, Bradycardia, Cardiac Arrhythmia, Phlebitis
Respiratory:	Bronchospasm, Wheezing, Hypoxemia
Dermatological:	Rash, Urticaria, Erythema, Injection Site Reaction
Nonspecific:	Prolonged Drug Effect
Neurologic:	Dizziness
Musculoskeletal:	Muscle Spasms

OVERDOSAGE: Overdosage with neuromuscular blocking agents may result in neuromuscular block beyond the time needed for surgery and anesthesia. The primary treatment is maintenance of a patent airway and controlled ventilation until recovery of normal neuromuscular function is assured. Once evidence of recovery from neuromuscular block is observed, further recovery may be facilitated by administration of an anticholinesterase agent (*e.g.*, neostigmine, edrophonium) in conjunction with an appropriate anticholinergic agent. (see **Antagonism of Neuromuscular Block**). Overdosage may increase the risk of hemodynamic side effects, especially decreases in blood pressure. If needed, cardiovascular support may be provided by proper positioning of the patient, fluid administration, and/or vasopressor agent administration.

Antagonism of Neuromuscular Block:

ANTAGONISTS (SUCH AS NEOSTIGMINE) SHOULD NOT BE ADMINISTERED WHEN COMPLETE NEUROMUSCULAR BLOCK IS EVIDENT OR SUSPECTED. THE USE OF A PERIPHERAL NERVE STIMULATOR TO EVALUATE RECOVERY AND ANTAGONISM OF NEUROMUSCULAR BLOCK IS RECOMMENDED.

Administration of 0.030 to 0.064 mg/kg neostigmine or 0.5 mg/kg edrophonium at approximately 10% recovery from neuromuscular block (range: 1 to 15) produced 95% recovery of the muscle twitch response and a T_4/T_1 ratio ≥75% in about 10 minutes. The times from 25% recovery of the muscle twitch response to T_4/T_1 ratio ≥75% following these doses of antagonists averaged about 7 to 9 minutes. In comparison, average times for spontaneous recovery from 25% to T_4/T_1 ≥75% were 12 to 13 minutes.

Patients administered antagonists should be evaluated for adequate clinical evidence of antagonism, *e.g.*, 5-second head lift and grip strength. Ventilation must be supported until no longer required.

Antagonism may be delayed in the presence of debilitation, carcinomatosis, and the concomitant use of certain broad spectrum antibiotics, or anesthetic agents and other drugs which enhance neuromuscular block or separately cause respiratory depression (see **Drug Interactions** subsection of PRECAUTIONS). Under such circumstances the management is the same as that of prolonged neuromuscular block (see OVERDOSAGE).

DOSAGE AND ADMINISTRATION: MIVACRON SHOULD ONLY BE ADMINISTERED INTRAVENOUSLY.

The dosage information provided below is intended as a guide only. Doses of MIVACRON should be individualized (see **Individualization of Dosages** subsection of CLINICAL PHARMACOLOGY). Factors that may warrant dosage adjustment include but may not be limited to: the presence of significant kidney, liver, or cardiovascular disease, obesity (patients weighing ≥30% more than ideal body weight for height), asthma, reduction in plasma cholinesterase activity, and the presence of inhalational anesthetic agents. The use of a peripheral nerve stimulator will permit the most advantageous use of MIVACRON, minimize the possibility of overdosage or underdosage, and assist in the evaluation of recovery.

Adults:

***Initial Doses*:**

A dose of 0.15 mg/kg MIVACRON administered over 5 to 15 seconds is recommended for facilitation of tracheal intubation for most patients. When administered as a component of a thiopental/opioid/nitrous oxide/oxygen induction-intubation technique, 0.15 mg/kg (2 x ED_{95}) MIVACRON produces generally good-to-excellent conditions for tracheal intubation in 2.5 minutes. Lower doses of MIVACRON may result in a longer time for development of satisfactory intubation conditions. Administration of MIVACRON doses above the recommended range (≥0.20 mg/kg) is associated with the development of transient decreases in blood pressure in some patients (see CLINICAL PHARMACOLOGY and ADVERSE REACTIONS).

STORAGE: Store MIVACRON Injection at room temperature of 15° to 25°C (59° to 77°F). Avoid exposure to direct ultraviolet light. DO NOT FREEZE.

Recommended storage for MIVACRON Premixed Infusion is room temperature (15° to 25°C/59° to 77°F). Avoid excessive heat. Avoid exposure to direct ultraviolet light. Protect from freezing.

U.S. Patent No. 4761418
January 1992
670002

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1. Savarese JJ, Ali HH, Basta SJ, et al. The clinical neuromuscular pharmacology of mivacurium chloride (BW B1090U): A short-acting nondepolarizing ester neuromuscular blocking drug. *Anesthesiology.* 1988;68:723-732.
2. Ali HH, Savarese JJ, Embree PB, et al. Clinical pharmacology of mivacurium chloride (BW B1090U) infusion: comparison with vecuronium and atracurium. *Br J Anaesth.* 1988;61:541-546.

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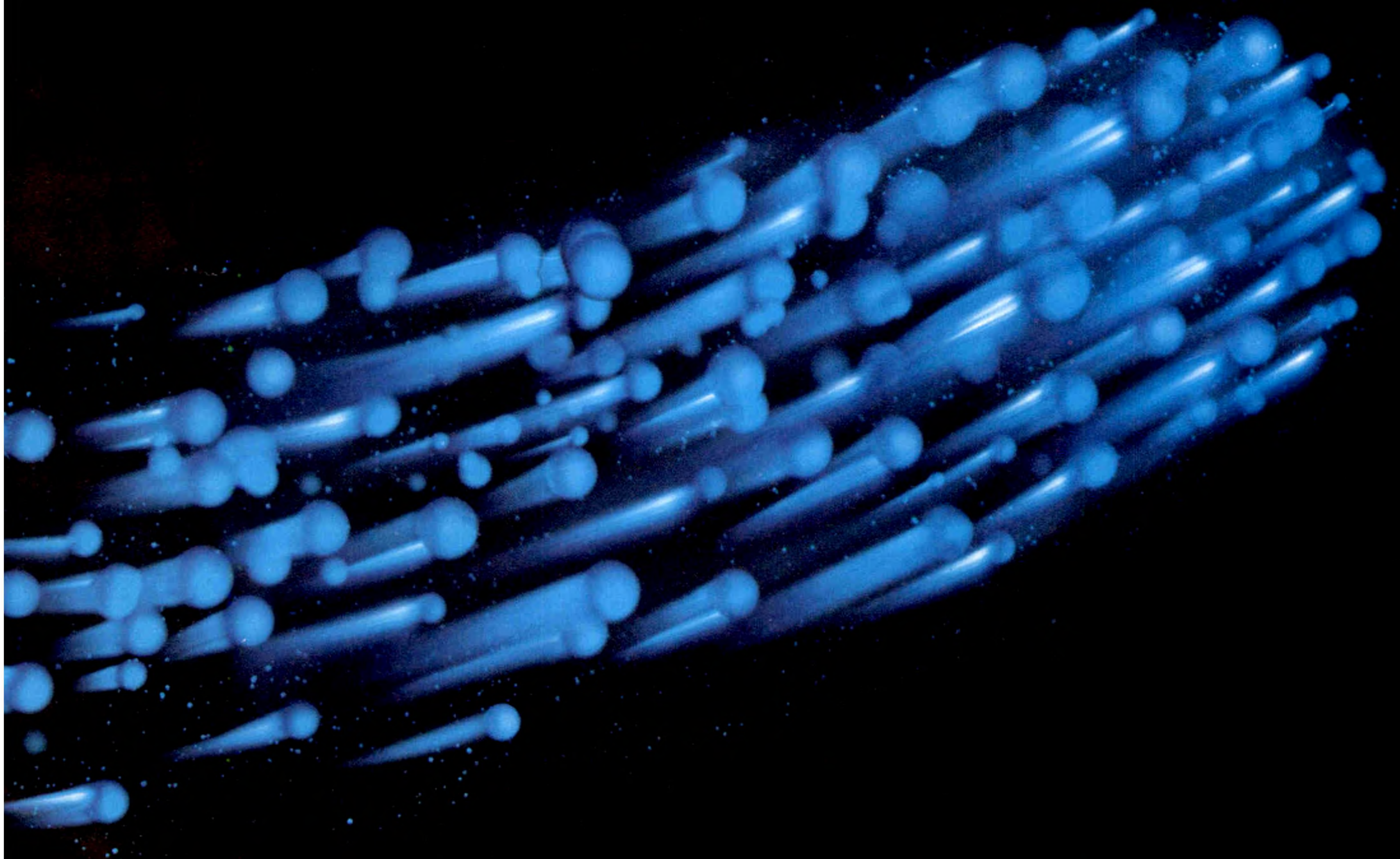

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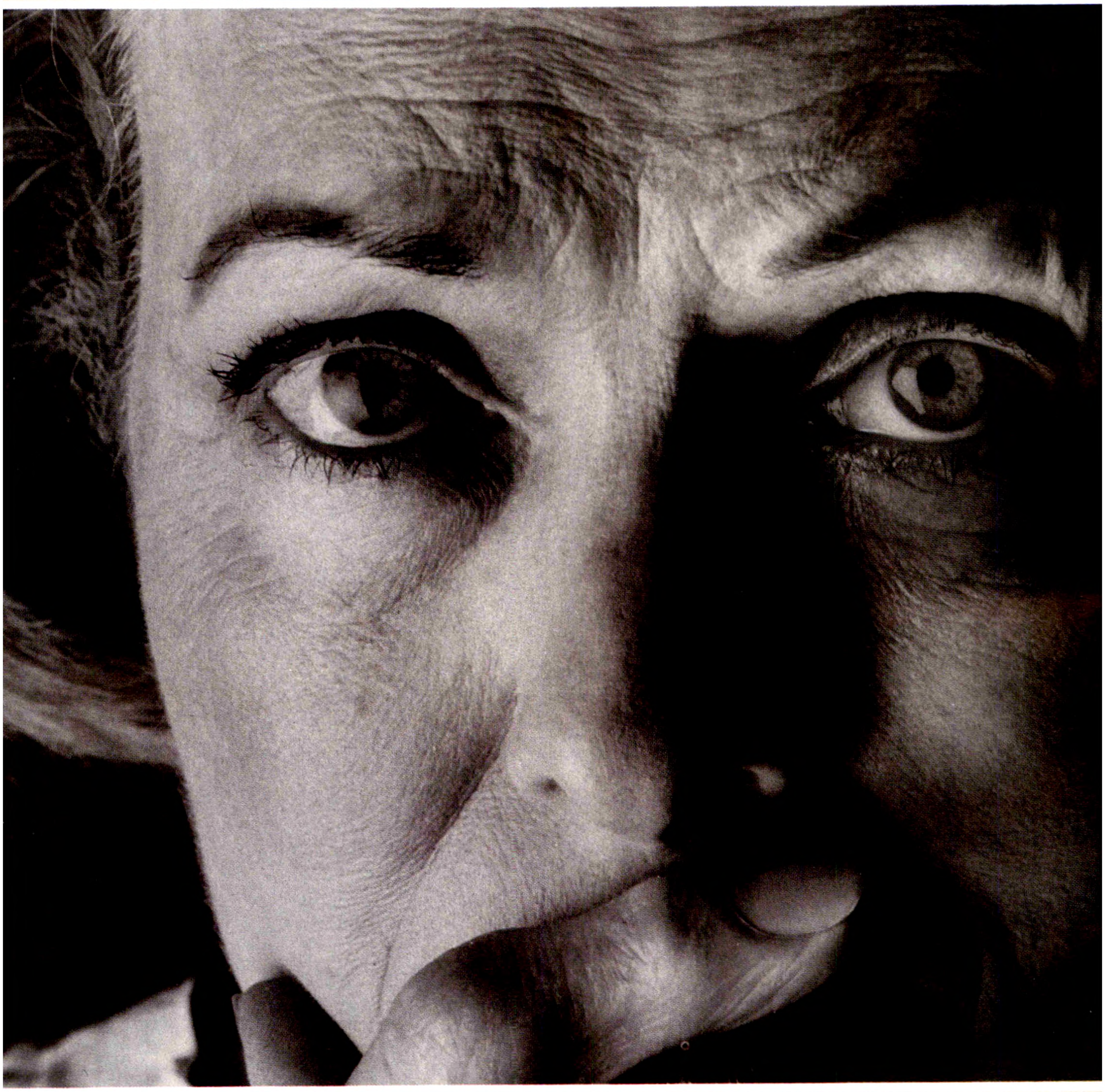

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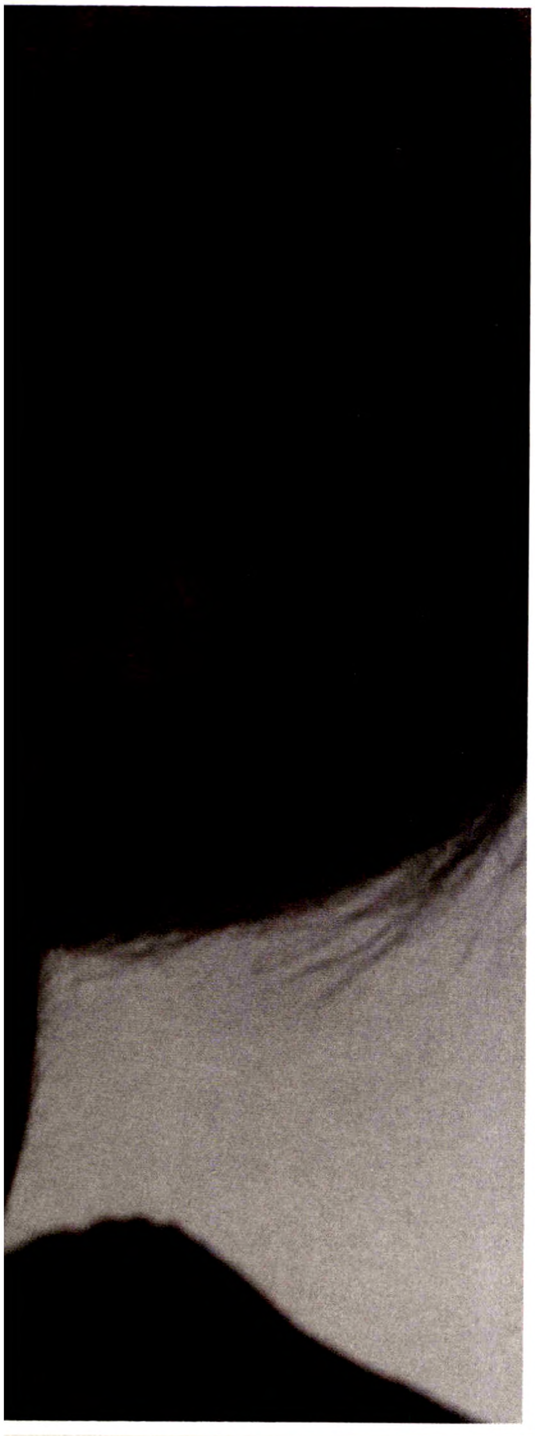

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References: **1.** Hespan® prescribing information. **2.** Waters LM, Christensen MA, Sato RM. Hetastarch: An alternative colloid in burn shock management. *J Burn Care Rehabil.* 1989;10:11-16. **3.** Rackow EC, Falk JL, Fein IA, et al. Fluid resuscitation in circulatory shock: A comparison of the cardiorespiratory effects of albumin, hetastarch, and saline solutions in patients with hypovolemic and septic shock. *Crit Care Med.* 1983;11:839-850.

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BRIEF SUMMARY

CONTRAINDICATIONS
HESPAN is contraindicated in patients with known hypersensitivity to hydroxyethyl starch, or with bleeding disorders, or with congestive heart failure where volume overload is a potential problem. HESPAN should not be used in renal disease with oliguria or anuria not related to hypovolemia.

WARNINGS
Usage in Plasma Volume Expansion: Large volumes may alter the coagulation mechanism. Thus, administration of HESPAN may result in transient prolongation of prothrombin, partial thromboplastin and clotting times. With administration of large doses, the physician should also be alert to the possibility of transient prolongation of bleeding time.

Hematocrit may be decreased and plasma proteins diluted excessively by administration of large volumes of HESPAN. Administration of packed red cells, platelets, and fresh frozen plasma should be considered if excessive dilution occurs.

Use over extended periods: HESPAN has not been adequately evaluated to establish its safety in situations other than leukapheresis that require frequent use of colloidal solutions over extended periods. Certain conditions may affect the safe use of HESPAN on a chronic basis. For example, in patients with subarachnoid hemorrhage where HESPAN is used repeatedly over a period of days for the prevention of cerebral vasospasm, significant clinical bleeding may occur.

Usage in Leukapheresis: Slight declines in platelet counts and hemoglobin levels have been observed in donors undergoing repeated leukapheresis procedures using HESPAN due to the volume expanding effects of HESPAN and to the collection of platelets and erythrocytes. Hemoglobin levels usually return to normal within 24 hours. Hemodilution by HESPAN and saline may also result in 24 hour declines of total protein, albumin, calcium and fibrinogen values. None of these decreases are to a degree recognized to be clinically significant risks to healthy donors.

PRECAUTIONS
General: Regular and frequent clinical evaluation and complete blood counts (CBC) are necessary for proper monitoring of HESPAN® (6% hetastarch in 0.9% sodium chloride injection) use during leukapheresis. If the frequency of leukapheresis is to exceed the guidelines for whole blood donation, you may wish to consider the following additional studies: total leukocyte and platelet counts, leukocyte differential count hemoglobin and hematocrit, prothrombin time (PT), and partial thromboplastin time (PTT) tests.

The possibility of circulatory overload should be kept in mind. Caution should be used when the risk of pulmonary edema and/or congestive heart failure is increased. Special care should be exercised in patients who have impaired renal clearance since this is the principal way in which hetastarch is eliminated.

Indirect bilirubin levels of 8.3 mg/L (normal 0.0 - 7.0 mg/L) have been reported in 2 out of 20 normal subjects who received multiple HESPAN infusions. Total bilirubin was within normal limits at all times; indirect bilirubin returned to normal by 96 hours following the final infusion. The significance, if any, of these elevations is not known; however, caution should be observed before administering HESPAN to patients with a history of liver disease.

HESPAN has been reported to produce hypersensitivity reactions such as wheezing and urticaria. However, hetastarch has not been observed to stimulate antibody formation. If hypersensitivity effects occur, they are readily controlled by discontinuation of the drug and, if necessary, administration of an antihistaminic agent.

Elevated serum amylase levels may be observed temporarily following administration of HESPAN, although no association with pancreatitis has been demonstrated.

If administration is by pressure infusion, all air should be withdrawn or expelled from the bag through the medication port prior to infusion.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies of animals have not been performed to evaluate the carcinogenic potential of hetastarch.

Teratogenic Effects: Pregnancy Category C. Animal reproduction studies have not been conducted with HESPAN. It is also not known whether HESPAN can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. HESPAN should be given to a pregnant woman only if clearly needed.

Nursing Mothers: It is not known whether hetastarch is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when HESPAN is administered to a nursing woman.

Pediatric Use: The safety and effectiveness of HESPAN in children have not been established.

ADVERSE REACTIONS
The following have been reported: vomiting, fever, chills, pruritus, submaxillary and parotid glandular enlargement, mild influenza-like symptoms, headaches, muscle pains, peripheral edema of the lower extremities, anaphylactoid reactions (periorbital edema, urticaria, wheezing), bleeding due to hemodilution (see *Warnings*), and circulatory overload and pulmonary edema (see *Precautions*).

DOSAGE AND ADMINISTRATION
Dosage for Acute Use in Plasma Volume Expansion: HESPAN® (6% hetastarch in 0.9% sodium chloride injection) is administered by intravenous infusion only. Total dosage and rate of infusion depend upon the amount of blood or plasma lost and the resultant hemoconcentration. In adults, the amount usually administered is 500 to 1000 mL. Doses of more than 1500 mL per day for the typical 70 kg patient (approximately 20 mL per kg of body weight) are usually not required, although higher doses have been reported in postoperative and trauma patients where severe blood loss has occurred.

Dosage in Leukapheresis: 250 to 700 mL of HESPAN to which citrate anticoagulant has been added is typically administered by aseptic addition to the input line of the centrifugation apparatus at a ratio of 1:8 to 1:13 to venous whole blood. The HESPAN and citrate should be thoroughly mixed to assure effective anticoagulation of blood as it flows through the leukapheresis machine.

Do not use plastic container in series connection.

If administration is controlled by a pumping device, care must be taken to discontinue pumping action before the container runs dry or air embolism may result.

This solution is intended for intravenous administration using sterile equipment. It is recommended that intravenous administration apparatus be replaced at least once every 24 hours.

Use only if solution is clear and container and seals are intact.

The safety and compatibility of other additives have not been established.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

If administration is by pressure infusion, all air should be withdrawn or expelled from the bag through the medication port prior to infusion.

HOW SUPPLIED
HESPAN® (6% hetastarch in 0.9% sodium chloride injection) is supplied sterile and nonpyrogenic in 500 mL EXCEL® Containers packaged 12 per case (NDC 0056-0037-46).

Exposure of pharmaceutical products to heat should be minimized. Avoid excessive heat. Protect from freezing. It is recommended that the product be stored at room temperature (25°C); however, brief exposure up to 40°C does not adversely affect the product.

CAUTION
Federal (USA) law prohibits dispensing without prescription.

To Open
Tear overwrap down at notch and remove solution container. Check for minute leaks by squeezing solution container firmly. If leaks are found, discard solution as sterility may be impaired.

Invert container and carefully inspect the solution in good light for cloudiness, haze, or particulate matter. Any container which is suspect should not be used.

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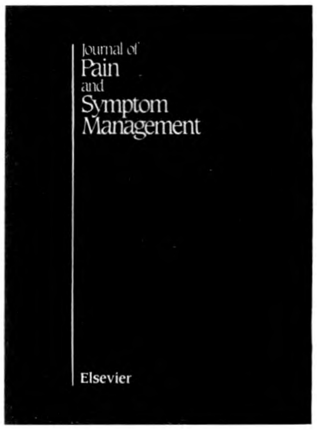

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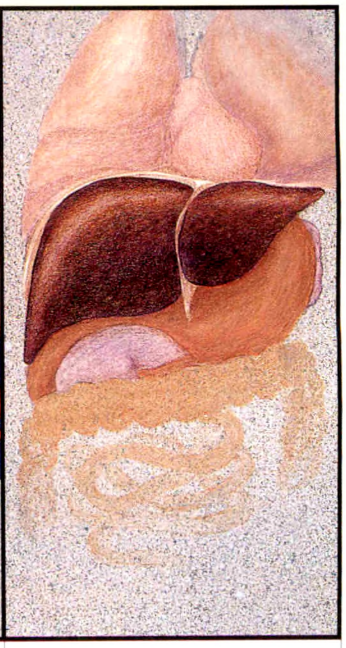

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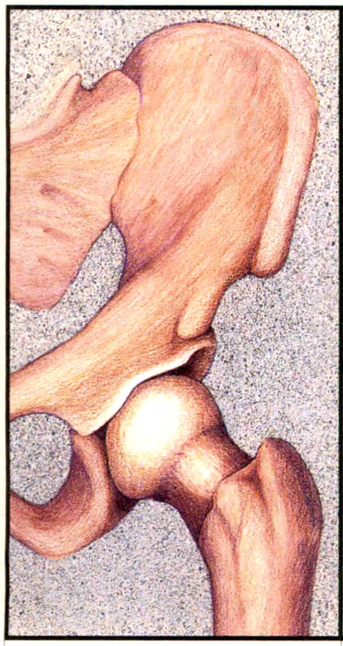
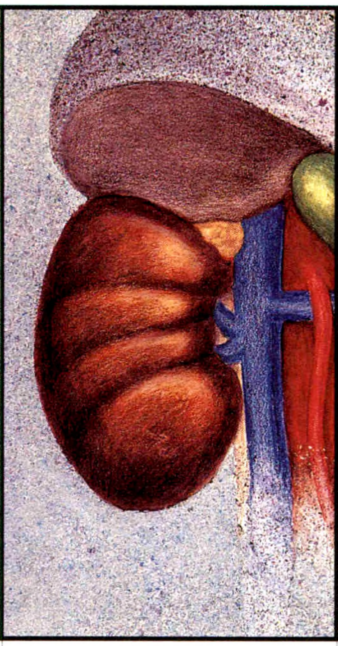
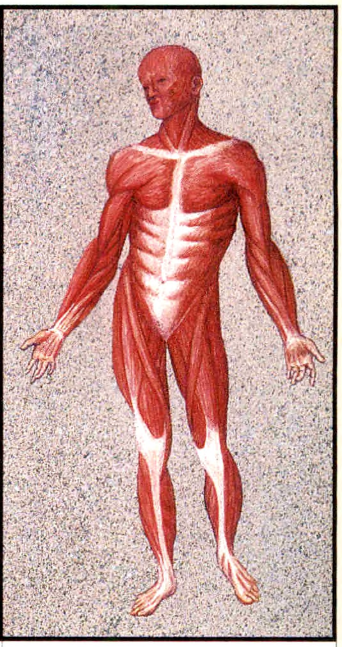
Common patient type Obese	**Common patient type** Both adults and children
Advantage of Tracrium No difference in recovery from neuromuscular blockade between normal and obese patients.[1]	**Advantage of Tracrium** Clinical response unaffected by hepatic function[2] or patient age.[3]







Total hip replacement	**Renal surgery**	**Neurosurgery for trauma**	**Everyday procedures**
Common patient type Elderly women and men	**Common patient type** Both adults and children	**Common patient type** Both adults and children	**Common patient type** Average
Advantage of Tracrium Recovery time unaffected by age.[3]	**Advantage of Tracrium** Recovery time unaffected by renal dysfunction.[2]	**Advantage of Tracrium** Effect unchanged by concomitant anticonvulsant medications (phenytoin, carbamazepine).[4,5]	**Advantage of Tracrium** The same reasons Tracrium is ideal for special patient types make it the choice for everyday procedures.

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INDICATIONS AND USAGE: Tracrium is indicated, as an adjunct to general anesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

CONTRAINDICATIONS: Tracrium is contraindicated in patients known to have a hypersensitivity to it.

WARNINGS: TRACRIUM SHOULD BE USED ONLY BY THOSE SKILLED IN AIRWAY MANAGEMENT AND RESPIRATORY SUPPORT. EQUIPMENT AND PERSONNEL MUST BE IMMEDIATELY AVAILABLE FOR ENDOTRACHEAL INTUBATION AND SUPPORT OF VENTILATION, INCLUDING ADMINISTRATION OF POSITIVE PRESSURE OXYGEN. ADEQUACY OF RESPIRATION MUST BE ASSURED THROUGH ASSISTED OR CONTROLLED VENTILATION. ANTICHOLINESTERASE REVERSAL AGENTS SHOULD BE IMMEDIATELY AVAILABLE. DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION. Tracrium has no known effect on consciousness, pain threshold, or cerebration. It should be used only with adequate anesthesia. Tracrium Injection, which has an acid pH, should not be mixed with alkaline solutions (e.g., barbiturate solutions) in the same syringe or administered simultaneously during intravenous infusion through the same needle. Depending on the resultant pH of such mixtures, Tracrium may be inactivated and a free acid may be precipitated. Tracrium Injection 10 mL multiple dose vials contain benzyl alcohol. Benzyl alcohol has been associated with an increased incidence of neurological and other complications in newborn infants which are sometimes fatal. Tracrium Injection 5 mL ampuls and 5 mL single use vials do not contain benzyl alcohol.

PRECAUTIONS: General: Although Tracrium is a less potent histamine releaser than d-tubocurarine or metocurine, the possibility of substantial histamine release in sensitive individuals must be considered. Special caution should be exercised in administering Tracrium to patients in whom substantial histamine release would be especially hazardous (e.g. patients with clinically significant cardiovascular disease) and in patients with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release. In these patients, the recommended initial Tracrium dose is lower (0.3 to 0.4 mg/kg) than for other patients and should be administered slowly or in divided doses over one minute. Since Tracrium has no clinically significant effects on heart rate in the recommended dosage range, it will not counteract the bradycardia produced by many anesthetic agents or vagal stimulation. As a result, bradycardia during anesthesia may be more common with Tracrium than with other muscle relaxants. Tracrium may have profound effects in patients with myasthenia gravis, Eaton-Lambert syndrome, or other neuromuscular diseases in which potentiation of nondepolarizing agents has been noted. The use of a peripheral nerve stimulator is especially important for assessing neuromuscular blockade in these patients. Similar precautions should be taken in patients with severe electrolyte disorders or carcinomatosis. Multiple factors in anesthesia practice are suspected of triggering malignant hyperthermia (MH), a potentially fatal hypermetabolic state of skeletal muscle. Halogenated anesthetic agents and succinylcholine are recognized as the principal pharmacologic triggering agents in MH-susceptible patients; however, since MH can develop in the absence of established triggering agents, the clinician should be prepared to recognize and treat MH in any patient scheduled for general anesthesia. Reports of MH have been rare in cases in which Tracrium has been used. In studies of MH-susceptible animals (swine) and in a clinical study of MH-susceptible patients, Tracrium did not trigger this syndrome. Resistance to nondepolarizing neuromuscular blocking agents may develop in burn patients. Increased doses of nondepolarizing muscle relaxants may be required in burn patients and are dependent on the time elapsed since the burn injury and the size of the burn. The safety of Tracrium has not been established in patients with bronchial asthma. **Long-Term Use in Intensive Care Unit (ICU):** Tracrium has been used to facilitate mechanical ventilation in ICU patients. When there is a need for long-term mechanical ventilation, the benefits to risk ratio of neuromuscular blockade must be considered. There is only limited information on the efficacy and safety of Tracrium administered by long-term (days to weeks) intravenous infusion to facilitate mechanical ventilation in intensive care facilities. For Tracrium, as with other neuromuscular blocking agents used in intensive care facilities, available evidence suggests that there is wide interpatient variability in dosage requirements and that these requirements may change with time. Limited data suggest that Tracrium infusion requirements may increase with prolonged administration in the ICU. As with other neuromuscular blocking agents, little information is available on the plasma levels or clinical consequences of atracurium metabolites following long-term (days to weeks) infusion of Tracrium in the intensive care unit setting. One metabolite of atracurium, laudanosine, when administered alone to laboratory animals, has been associated with cerebral excitatory effects. Physiological effects of laudanosine in humans have not been demonstrated. The effects of hemodialysis, hemoperfusion and hemofiltration on plasma levels of atracurium and its metabolites are unknown. **Drug Interactions:** Drugs which may enhance neuromuscular blocking action of Tracrium include: enflurane; isoflurane; halothane; certain antibiotics, especially the aminoglycosides and polymyxins; lithium; magnesium salts; procainamide; and quinidine. If other muscle relaxants are used during the same procedure, the possibility of a synergistic or antagonist effect should be considered. The prior administration of succinylcholine does not enhance the duration, but quickens the onset and may increase the depth, of neuromuscular blockade induced by Tracrium. Tracrium should not be administered until a patient has recovered from succinylcholine-induced neuromuscular blockade. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** A positive response was observed in the mouse lymphoma assay under conditions which killed over 80% of the treated cells. A far weaker response was observed in the presence of metabolic activation at concentrations which also killed over 80% of the treated cells. **Pregnancy:** ***Teratogenic Effects:*** Pregnancy Category C. Tracrium has been shown to be potentially teratogenic in rabbits, when given in doses up to approximately one-half the human dose. There are no adequate and well-controlled studies in pregnant women. Tracrium should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Labor and Delivery:** It is not known whether muscle relaxants administered during vaginal delivery have immediate or delayed adverse effects on the fetus or increase the likelihood that resuscitation of the newborn will be necessary. The possibility that forceps delivery will be necessary may increase. Tracrium (0.3 mg/kg) has been administered to 26 pregnant women during delivery by cesarean section. No harmful effects were attributable to Tracrium in any of the newborn infants, although small amounts of Tracrium were shown to cross the placental barrier. The possibility of respiratory depression in the newborn infant should always be considered following cesarean section during which a neuromuscular blocking agent has been administered. In patients receiving magnesium sulfate, the reversal of neuromuscular blockade may be unsatisfactory and Tracrium dose should be lowered as indicated. **Nursing Mothers:** It is not known whether this drug is excreted in human milk. Caution should be exercised when Tracrium is administered to a nursing woman. **Pediatric Use:** Safety and effectiveness in children below the age of 1 month have not been established.

ADVERSE REACTIONS: Observed in Controlled Clinical Studies: Tracrium produced few adverse reactions during extensive clinical trials. Most were suggestive of histamine release (see Precautions Section). The overall incidence rate for clinically important adverse reactions was 7/875 or 0.8%. Most adverse reactions were of little clinical significance unless they were associated with significant hemodynamic changes. Substantial vital sign changes greater than or equal to 30% observed in 530 patients, without cardiovascular disease, were as follows: in those patients given the recommended initial dosage range of 0.31 to 0.50 mg/kg of Tracrium, mean arterial pressure increased in 2.8% and decreased in 2.1% of patients while the heart rate increased in 2.8% of these patients. At doses of ≥ 0.60 mg/kg, 14.3% of the studied patients had a decrease in mean arterial pressure while 4.8% had an increase in heart rate. At doses ≤ 0.30 mg/kg, mean arterial pressure increased in 1.9% and decreased in 1.1% of patients, while heart rate increased in 1.6% and decreased in 0.8% of these patients. **Observed in Clinical Practice:** Based on clinical experience in the U.S. and the United Kingdom of approximately 3 million patients given Tracrium the following adverse reactions are among the most frequently reported: *General:* allergic reactions (anaphylactic or anaphylactoid) which, in rare instances, were severe (e.g., cardiac arrest); *Musculoskeletal:* inadequate, prolonged block; *Cardiovascular:* hypotension, vasodilatation (flushing), tachycardia, bradycardia; *Respiratory:* dyspnea, bronchospasm, laryngospasm; *Integumentary:* rash, urticaria, injection site reaction.

STORAGE: Tracrium Injection should be refrigerated at 2° to 8° C (36° to 46° F) to preserve potency. DO NOT FREEZE. Upon removal from refrigeration to room temperature storage conditions (25° C/77° F), use Tracrium Injection within 14 days even if rerefrigerated.

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Oculopharyngeal Dystrophy: An Approach to Anesthetic Management

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Oculopharyngeal dystrophy is a rare variant of muscular dystrophy characterized by progressive dysphagia and ptosis (1). There have been a few reported cases of ocular myopathy with unusual sensitivity to succinylcholine (2) and to *d*-tubocurarine (3–5) and lack of response to anticholinesterases (3–5). There have been no reports in the anesthesia literature, however, of patients with oculopharyngeal dystrophy. This is the first report describing the anesthetic management of a patient with oculopharyngeal dystrophy.

Case Report

A 72-y-old woman with oculopharyngeal dystrophy was scheduled to undergo therapeutic cricopharyngeal myotomy. Her symptoms included recurrent aspiration of gastric contents, difficulty in swallowing, and a recent 25-kg weight loss over the previous 2 mo.

This patient had had mild dysphagia since age 15 yr that had become progressively worse during the previous year so that she could no longer swallow liquids or solids. She had had drooping eyelids for at least 35 yr. Other medical problems included hypertension for 10 yr and a productive cough for 2 yr. She had smoked for 50 yr. Surgical history included a cholecystectomy approximately 30 yr earlier under general anesthesia without any problems and eyelid surgery 4 yr earlier under local anesthesia.

Family members with a history of ptosis and dysphagia included the patient's mother, two brothers, two maternal uncles, and one son. Her two sisters did not have any symptoms of the condition. The patient reported that the condition was "brought from overseas," but she did not know the country of origin. Her mother had lived past the age of 70 yr but had developed severe weakness. When she died, there was food found in her throat. One of her brothers who had ptosis and dysphagia required mechanical ventilation before his death. The patient had seven children; however, only one son, age 57 yr, had developed symptoms of ptosis and dysphagia.

On physical examination, she was cachectic, weighed 36 kg, and measured 170 cm in height. She had bilateral ptosis, but extraocular movements were intact. She also had temporal muscle wasting and muscle wasting of the extremities; however, muscle strength and deep tendon reflexes were normal, as were serum creatinine phosphokinase and serum aldolase levels.

Other preoperative laboratory data were reported to be normal, except for arterial pH 7.40, $Paco_2$ 46 mm Hg, Pao_2 60 mm Hg, arterial O_2 saturation 91%, and fraction of inspired O_2 0.2.

A chest radiograph showed a wide lucency terminating at the clavicular level that was probably pharyngeal/cervical esophagus. An esophageal transit/gastrointestinal reflux study revealed markedly delayed pharyngeal and esophageal motility and evidence of right bronchial aspiration. On Holter monitoring, a wandering atrial pacemaker was evident.

Because of the history of ptosis and her progressive dysphagia, a diagnosis of myasthenia gravis was considered. A nerve conduction study with repetitive stimulation at 2 and 20 Hz did not reveal any decrementing response, and a single-fiber electromyograph showed no increased "jitter." A decrementing response on the nerve conduction study and "jitter," or blocking, of successive discharges from single-motor fibers belonging to the same motor unit would have been electrophysiologic evidence for myasthenia gravis (6). An edrophonium test was requested but not completed during this hospital stay. In patients with myasthenia gravis, there is a deficiency of acetylcholine receptors at the neuromuscular junction as a result of antibodies to acetylcholine receptor protein (6). Edrophonium inhibits the enzyme acetylcholinesterase, so that there is an excess of acetylcholine to intereact repeatedly with the limited number of acetylcholine receptors. After an intravenous dose of 2.0 mg, if muscle strength improves within 30 s, the test is considered positive for myasthenia gravis. If there is no response with a dose of 2.0 mg, an additional 8.0 mg can be administered intravenously. Muscle strength will improve visibly within 30 s and decrease after 5 min if the patient has myasthenia gravis (7).

The results of the nerve conduction studies and single-fiber electromyogram, the history of dysphagia, the clinical findings of bilateral ptosis and cachexia due to the dysphagia, and the significant family history all confirmed the diagnosis of oculopharyngeal dystrophy.

Before the procedure, the patient received no preanes-

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thetic medications. In the operating room, routine monitors were used, and neuromuscular blockade was monitored at the masseter muscle. After breathing oxygen via a mask, anesthesia was induced with 25 μg of fentanyl, 35 mg of lidocaine, and 75 mg of thiopental. After the application of cricoid pressure and the establishment of a patent airway by mask, 3.5 mg of vecuronium was administered intravenously, and the trachea was subsequently intubated. The anesthetic was maintained with oxygen (2 L/min), N_2O (3 L/min), and isoflurane (0.5%–1.0%). One hour after induction when she had four detectable responses to train-of-four stimulation, the patient received an additional 1.0 mg of vecuronium. At the conclusion of the procedure (approximately 150 min after the intubating dose of vecuronium), and after the patient had demonstrated return of all four twitches with train-of-four stimulation at the masseter muscle, neostigmine (3.0 mg IV) and glycopyrrolate (0.5 mg IV) were administered. After she was able to open her eyes and lift her head, the endotracheal tube was removed, and she was transported to the recovery room, with oxygen via face mask. Her postoperative course was uncomplicated.

Discussion

The muscular dystrophies represent a group of muscle disorders that are progressive, hereditary, degenerative diseases of the skeletal muscles (8). The dystrophies are thought to be mainly disorders of muscle fiber, because patients with muscular dystrophy demonstrate intact spinal motor neurons, nerves, and nerve endings, although the muscle fibers are severely degenerated (8). Characteristic features of this group of diseases include symmetric distribution of weakness and atrophy, intact sensation, preservation of reflexes, and a family history of the disorder (8).

Oculopharyngeal muscular dystrophy is a rare variant of muscular dystrophy first described in 1962 by Victor et al. (1). This syndrome of ocular ptosis and dysphagia has an autosomal dominant mode of inheritance. Onset is insidious, usually late in life, and progression is slow (1). Dysphagia usually precedes ptosis. This slowly progressive myopathic process primarily involves the levator palpebrae muscles, pharynx, hypopharynx and, upper one-third of the esophagus (9), with only the striated muscle of the esophagus disturbed (10). Some patients have also displayed weakness in the neck flexors and limb girdle muscles (9).

Cases of ocular dystrophy have been described in the anesthesia literature. Ocular dystrophy is manifested by ptosis and extraocular muscle weakness but not dysphagia (3–5). The presence of extraocular muscle weakness distinguishes ocular dystrophy from oculopharyngeal dystrophy. The patient described in our report had ptosis and dysphagia but not extraocular muscle weakness, so that her condition represents a case of oculopharyngeal dystrophy.

Special considerations in the anesthetic management of patients with oculopharygneal dystrophy include their dysphagia, which may increase their risk of aspiration, their response to neuromuscular relaxants and anticholinesterases, their pulmonary status preoperatively, and their respiratory muscle strength postoperatively. Our patient had clinical evidence of pooling of secretions in the piriform recesses, delayed pharyngeal emptying, and right bronchial aspiration on her gastroesophageal reflux scan. For these reasons, we chose to use cricoid pressure during our induction of anesthesia to help prevent aspiration of secretions.

Patients with neuromuscular disorders have exhibited varied responses to depolarizing and nondepolarizing muscle relaxants (11). Dresner and Ali (12) recently described a patient with facioscapulohumeral dystrophy who had a much faster than normal recovery from atracurium blockade. There has been a report of a 48-yr-old woman with ocular myopathy who exhibited unusual sensitivity to succinylcholine. A dose of 20 mg administered intravenously resulted in 60 min of apnea (2). Another report describes a 7-yr-old boy with ocular muscular dystrophy who demonstrated extreme sensitivity to *d*-tubocurarine, with lack of reversal by anticholinesterases. This patient had received succinylcholine on two previous occasions without any adverse reaction (5). Ross (3) in 1963 described four patients with ocular myopathy who exhibited extreme sensitivity to *d*-tubocurarine. He concluded that these patients had a form of progressive muscular dystrophy with abnormal sensitivity to *d*-tubocurarine. Their ptosis did not respond to prostigmine, as would have been expected if they had myasthenia gravis (3). Later, in 1966, Jacob and Varkey (4) described four more patients with ocular myopathy who exhibited unusual sensitivity to *d*-tubocurarine and no response to anticholinesterases. Both Ross (3) and Jacob and Varkey (4) used a *d*-tubocurarine test to evaluate neuromuscular transmission in these patients with ocular myopathies to determine whether they had myasthenia gravis.

The *d*-tubocurarine test as used by Ross (3) and Jacob and Varkey (4) has been used to study neuromuscular transmission in patients with primary disorders of nerve or muscle. In 1975, Brown et al. (13) described a regional technique to study *d*-tubocurarine sensitivity. This technique allowed the use of a reduced dose of *d*-tubocurarine to be injected into an ischemic limb. The effects on muscle strength in that limb alone could then be studied by measuring evoked muscle action potential amplitudes. Recovery usually occurs during the 20–30 min after release of the tourniquet. This technique allows assessment of the reserve of the neuromuscular junction when there is no evidence of a clinical disorder. The authors caution that whenever this test is performed, there should be staff and equipment immediately available to assist ventilation, because there is always the risk of respiratory arrest, even with very small doses of *d*-tubocurarine (13).

The use of the depolarizing muscle relaxant succinylcholine in patients with muscular dystrophy can be associated with serious complications. There has been the previously mentioned report of extreme sensitivity in a woman with ocular dystrophy (2). There have been several reports of rigidity (14), rhabdomyolysis (15), myoglobinuria (15,16), malignant hyperthermia (16–19), and cardiac arrest (20–22) in children with Duchenne's muscular dystrophy. In this case, we chose to use the nondepolarizing muscle relaxant vecuronium during induction to aid intubation; however, we might have either avoided using any muscle relaxants or used a much smaller dose.

Preoperative pulmonary status should be evaluated carefully because some of these patients may have weakness of the limb girdle muscles (9) that could lead to the need for mechanical ventilation postoperatively. Our patient did have mild carbon dioxide retention with an oxygen saturation of 91% while breathing room air, indicative of underlying pulmonary disease. She did not have any evidence of limb girdle weakness. Before tracheal extubation, she was able to open her eyes and lift her head for 5 s, which indicated adequate muscle strength to ventilate postoperatively. In the recovery room before discharge, her oxygen saturation was 96% on room air.

In summary, this report describes the anesthetic management of a patient with oculopharyngeal dystrophy, a rare form of progressive muscular dystrophy that has not been previously described in the anesthesia literature.

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Bilateral Interpleural Injection of Lidocaine After Bilateral Lung Surgery Through Median Sternotomy in Four Patients

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Unilateral interpleural analgesia has been used to provide pain relief in a variety of clinical situations; however, its usefulness for postthoracotomy pain relief still remains controversial (1). In addition, Kambam et al. (2) reported that unilateral interpleural administration of bupivacaine produces no pain relief after anterior thoracotomy.

There have been a few reports describing the effects of bilateral interpleural analgesia for pain relief after abdominal surgery and thoracic pain secondary to carcinoma and multiple rib fractures (3,4). However, the analgesic effects and pharmacokinetics of the bilateral technique with lidocaine after median sternotomy are unknown.

We describe four patients in whom lidocaine was administered into both pleural spaces for postoperative pain relief after bilateral lung surgery through median sternotomy. In these patients, the degree of pain was assessed, and the plasma concentrations of lidocaine were determined after bilateral injection of lidocaine with epinephrine.

Case Reports

The present study was approved by the Ethical Committee of our institute, and informed consent was obtained from each patient. Table 1 displays the demographic characteristics of the four patients. Analgesic assessment and measurement of the plasma levels of lidocaine were performed before and 5, 10, 20, 30, 60, 90, 120, 150, and 180 min after the injection. The arterial plasma levels of lidocaine were measured by enzyme immunoassay, as described previously by Pape et al. (5). The degree of postoperative pain was evaluated with a visual analogue scale (VAS) (0 mm = no pain; 100 mm = intolerable pain). The extent of analgesia was assessed by the pinprick test. The duration of analgesia was defined as the time from the injection of lidocaine until the patient again complained of pain. The arterial blood pressure (BP), heart rate (HR), and respiratory rate (RR) were continuously recorded. Analysis of arterial blood gases was performed before and after the injection. The time-course of VAS values and plasma levels of lidocaine in the four study patients are shown in Figures 1–3.

Patient 1

This patient was scheduled for wedge resection of each of the upper lobes for metastatic pulmonary lesions due to carcinoma of the ascending colon. Premedication consisted of atropine (0.5 mg) and hydroxyzine (50 mg) administered intramuscularly. Anesthesia was induced with intravenous thiamylal followed by intravenous succinylcholine to facilitate endotracheal intubation. Anesthesia was maintained with halothane (0.6%–2.5%) and nitrous oxide (60%–70%) in oxygen, supplemented with intravenous pancuronium. No systemic opioids were administered during surgery. Bilateral thoracotomy was performed through median sternotomy. Before chest closure, an 18-gauge nylon epidural catheter was inserted 10 cm into each pleural space through a 16-gauge Tuohy needle at the seventh intercostal space 5 cm posterior from the midaxillary line of both sides. The catheter tip was positioned posterolaterally, and chest tubes were anterolaterally inserted into both pleural spaces, according to McIlvaine et al. (6). Ten milliliters of 1.5% lidocaine with 1:200,000 epinephrine was injected into each side via the interpleural catheter in the supine position when the patient was alert and complained of pain after the trachea was extubated. Both chest tubes were clamped for 10 min.

The VAS value preinjection was 82 mm and decreased to 8 mm at 30 min after the injection (Figure 1). The maximal extent of analgesia was T4-8, and duration of analgesia was 3.8 h. The maximal concentration of lidocaine in plasma (Cmax) was 3.60 μg/mL, occurring at 10 min after the injection (Figure 2). No significant changes in BP, HR, or RR were observed either before or after the injection. Before the injection, $Paco_2$ and Pao_2 were 44 and 123 mm Hg, respectively, under the face mask (inspired O_2 concentration, 0.4). One hour after the injection, $Paco_2$ decreased to 38 mm Hg and Pao_2 increased to 143 mm Hg under the face mask (inspired O_2 concentration, 0.4).

Patient 2

This patient underwent bilateral bullectomy of bullae of the lower lobes through median sternotomy. Anesthesia was induced, and interpleural catheters were placed in the same

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Table 1. Clinical Characteristics of the Four Study Patients

	Patient 1	Patient 2	Patient 3	Patient 4
Age (yr)/gender	37/F	17/M	67/F	63/M
Weight (kg)	38	45	45	46
Height (cm)	154	148	148	158
Medical diagnosis	Bilateral metastatic pulmonary carcinoma	Bilateral bullae	Bilateral metastatic pulmonary carcinoma	Bilateral metastatic pulmonary carcinoma
Operation	Wedge resection of bilateral upper lobes	Bilateral bullectomy	Wedge resection of bilateral upper lobes	Wedge resection of bilateral lower lobes
Anesthesia	Halothane/N_2O	Halothane/N_2O	Halothane/N_2O	Isoflurane/N_2O

F, female; M, male.

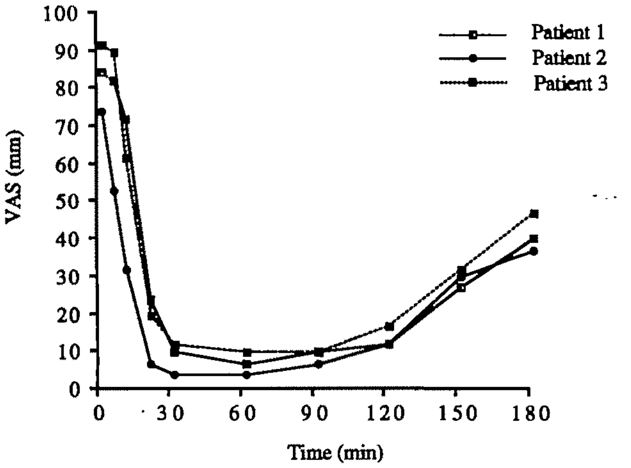

Figure 1. Time-course of visual analogue scale (VAS) (0–100 mm) after the injection of 10 mL of 1.5% lidocaine with 1:200,000 epinephrine into each pleural space in patients 1–3.

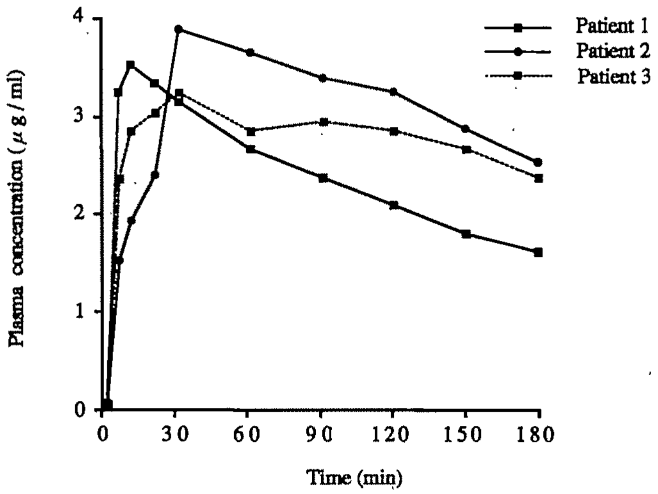

Figure 2. Plasma concentrations of lidocaine after the injection of 1.5% lidocaine with epinephrine (10 mL) into each pleural space in patients 1–3.

manner as described for patient 1. No systemic opioids were administered during the surgery. Ten milliliters of 1.5% lidocaine with 1:200,000 epinephrine was injected into each pleural space via the interpleural catheters when the patient complained of postoperative pain, and both chest tubes were clamped for 10 min. The VAS value preinjection was 72 mm and decreased to 5 mm at 20 min after the injection (Figure 1). The maximal extent of analgesia was T4-8, and duration of analgesia was 3.5 h. The Cmax of lidocaine was 3.87 μg/mL, occurring at 30 min after the injection (Figure 2). No changes in BP, HR, or RR either before or after the injection were observed. Preinjection, Pa_{O_2} and Pa_{CO_2} were 39 and 74 mm Hg in room air, respectively. One hour after the injection, Pa_{CO_2} decreased to 35 mm Hg and Pa_{O_2} increased to 81 mm Hg in room air.

Patient 3

This patient underwent bilateral wedge resection of the upper lobes through median sternotomy for metastatic pulmonary lesions due to carcinoma of the ascending colon. Anesthesia was performed in the same manner as described for patient 1. No systemic opioids were administered during surgery. At the end of surgery, bilateral interpleural catheters were placed in the same manner as described for patient 1. Ten milliliters of 1.5% lidocaine with 1:200,000 epinephrine was injected into each pleural space when the patient requested relief of postoperative pain, and both chest tubes were clamped for 10 min. The VAS value before the injection was 90 mm and decreased to 18 and 10 mm at 20 and 30 min after injection, respectively (Figure 1). The maximal extent of analgesia was T2-10, and duration of analgesia was 4.0 h. The Cmax of lidocaine in the plasma was 3.30 μg/mL, occurring 30 min after injection (Figure 2). No changes in BP, HR, RR, or arterial blood gases either before or after the injection were observed.

Patient 4

This patient was scheduled for bilateral wedge resection of the lower lobes through median sternotomy for metastatic pulmonary lesions due to adenocarcinoma of the kidney. Anesthesia was induced in the same manner as described for patient 1 and was maintained with isoflurane (0.8%–3.0%) and nitrous oxide (60%–70%) in oxygen, supplemented with intravenous vecuronium. No systemic opioids were administered during surgery. Bilateral interpleural catheters were placed after surgery, and 10 mL of 1.5% lidocaine with epinephrine was injected into each pleural space in the same manner as described for patient 1. Both chest tubes were clamped for 10 min. The 82-mm VAS value at preinjection decreased to 10 mm at 10 min after the

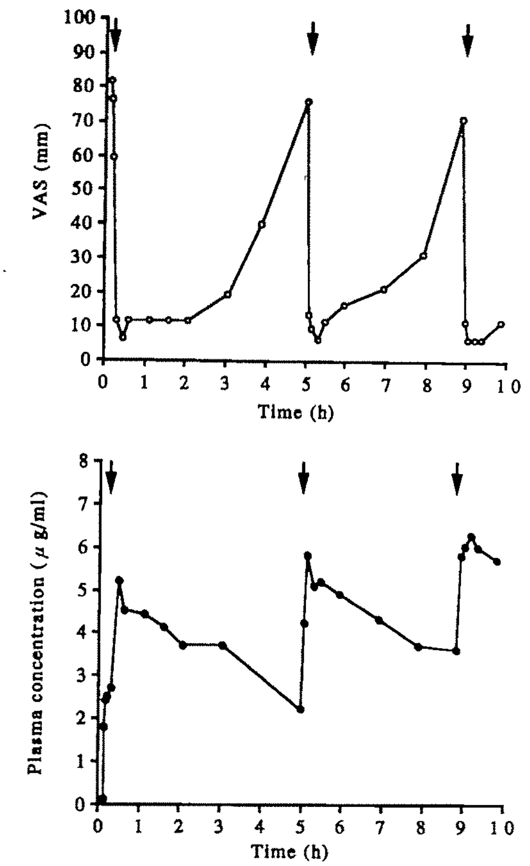

Figure 3. Time-course of visual analogue scale (VAS) (*upper panel*) and plasma concentrations of lidocaine (*lower panel*) during bilateral interpleural "topping-up" injection in patient 4. *Left arrow,* injection of 10 mL of 1.5% lidocaine with 1:200,000 epinephrine through each catheter; *middle and right arrows,* injection of 7.5 mL of 1.5% lidocaine with epinephrine into each pleural space.

injection. The VAS values did not exceed 20 mm for 3 h (Figure 3). When the patient complained of pain again (5 h after injection), 7.5 mL of 1.5% lidocaine with epinephrine was injected into each pleural space, and both chest tubes were clamped for 10 min. The second injection provided excellent pain relief, and the VAS values showed 5–8 mm; however, the patient showed incoherent speech, followed by drowsiness. Four hours after the second injection, the patient complained of pain (VAS 70 mm), and another 7.5 mL of 1.5% lidocaine with epinephrine was injected into each pleural space, and both chest tubes were clamped for 10 min. Although the VAS values decreased to 5 mm (Figure 3), the early signs of lidocaine toxicity of muscular tremor and incoherent speech, followed by drowsiness, appeared.

The time-course of the plasma concentrations of lidocaine in patient 4 is also shown in Figure 3. The initial Cmax was 5.1 µg/mL, occurring at 20 min after the initial injection, and when the patient complained again, the plasma concentration had decreased to 2.1 µg/mL. The Cmax of lidocaine was 5.7 µg/mL at 10 min after the second injection. The concentration of lidocaine was 3.5 µg/mL when the patient subsequently complained of pain (VAS 70 mm), and Cmax after the third injection was 6.2 µg/mL. No changes in BP, HR, RR, or arterial blood gas tensions either before or after the injection were observed.

Discussion

Median sternotomy has recently gained popularity as an approach for the excision of bilateral multiple metastatic pulmonary nodules and bilateral pulmonary bullous disease (7). Pain management after thoracotomy is important not only to ensure the patient's comfort, but also to minimize pulmonary complications. Systemic opioid administration has been the frequently utilized treatment for postthoracic surgery. Appropriate opioid use achieves a balance between adequate patient comfort and avoidance of excessive sedation or respiratory depression. However, some reports have documented that the analgesia produced by intercostal nerve blocks or epidural anesthesia is superior to that produced by conventional opioid analgesia (8,9). Although epidural local anesthetic administration would appear to solve the problem of postoperative pain in patients after sternotomy, this technique produces hypotension, and epidural opiates cause respiratory depression.

Interpleural analgesia is clinically useful in pain management after lateral and posterior thoracotomy (2). Lack of sympathetic blockade, systemic hypotension, and respiratory depression are the advantages of interpleural blockade compared with epidural blockade. In addition, phrenic nerve palsy associated with interpleural analgesia is less likely in humans (10). With regard to the mechanism of analgesia produced by this technique, it has been suggested that the local anesthetic solution diffuses from the pleural space through the parietal pleura and the innermost intercostal muscle to reach the intercostal space, where blockade of the intercostal nerves occurs unilaterally (11). On the other hand, because the terminal ends of the intercostal nerves often pass the midline to the opposite side (12), the technique of bilateral anterior intercostal nerve blocks of eight or more is necessary to relieve the pain of sternotomy or fracture of the sternum (1). Accordingly, bilaterial interpleural injection of local anesthetics may be useful to provide pain relief after median sternotomy. These case reports demonstrate that bilateral interpleural injection of lidocaine with epinephrine was effective against postoperative pain for >3 h without systemic administration of analgesics in patients who had undergone bilateral lung surgery through median sternotomy. The Cmax of bupivacaine of the unilateral interpleural blockade in patients who have undergone thoracotomy has been reported to be as low as 1.2 µg/mL and as high as 3.2 µg/mL (13–15). The arterial plasma level of bupivacaine associated with central nervous system toxicity is generally 2–4 µg/mL (16). Therefore, the plasma concentration of bupivacaine after bilateral interpleural block with bupivacaine will exceed the limits, resulting in convulsion and cardiac depression. It has been reported that bilateral interpleural injection of 20 mL of 0.75% bupivacaine with epinephrine provides profound, prolonged, and repeatable pain relief after midline and across-midline abdominal surgical interventions; however, the injection of 20 mL of 0.5% bupivacaine with epinephrine is ineffective, and, furthermore, the mean plasma concentration of bupivacaine after bilateral injection of 30 mL of 0.75% bupivacaine with epinephrine has been above the toxic level (3). These results suggest that the differences between doses that are ineffective and those that are toxic may be small with regard to bilateral interpleural analgesia.

We used this technique with lidocaine because of the rapid onset of analgesia with only slight cardiovascular depression. Although no clinical signs of local anesthetic toxicity were observed in our patients after the initial injection of 10 mL of 1.5% lidocaine with 1:200,000 epinephrine into each side, the Cmax of lidocaine showed 3.3–5.1 μg/mL, which seems to be relatively high. Furthermore, in patient 4, an initial peak plasma level of lidocaine was achieved in 20 min, followed by a slow decay, so that 180 min after the initial injection, the plasma level was 70% of the peak value. With two subsequent injections, peak levels increased above those of the preceding injections, the third values ranging from 5.3 to 6.2 μg/mL. Thus, it was likely that the lidocaine accumulated to a significant level in plasma and clinically produced the early toxic signs corresponding to the plasma level. Although the occurrence of cumulative toxicity as a result of repeat injections of local anesthetics has been reported in relation to epidural anesthesia (17), it has not been well appreciated with regard to interpleural analgesia. Rosenberg et al. (18) demonstrated that the plasma concentrations of bupivacaine rise markedly during continuous interpleural infusion and that after a 2-day infusion, are at a level regarded as toxic in humans. This suggests that caution may be necessary to avoid cumulative toxicity with repeat injections of local anesthetics in bilateral as well as unilateral interpleural analgesia.

In conclusion, bilateral interpleural blockade with lidocaine was effective against postoperative pain in the early phase after bilateral lung surgery through median sternotomy in the four patients presented here. However, these cases also showed that the peak plasma concentrations of lidocaine were relatively high after the initial injection and, furthermore, that repeat injections produced early toxic signs, with plasma concentrations nearly at the toxic level. From the clinical point of view, this case report suggests the need for cautious administration of bilateral interpleural lidocaine as well as bupivacaine. Further studies are needed to examine dosage regimens for this technique and to compare it with other ways of achieving analgesia (e.g., systemic opioids, epidural opioids, intercostal blocks).

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A Fractured Epidural Needle: Case Report and Study

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Epidural blocks are most commonly performed using a 17-gauge needle to permit easy passage of the catheter. The durability of these large-gauge needles can be inferred by the lack of any reports of breakage other than separation at the hub-needle shaft junction (1). Recent improvements in catheter technology and the availability of smaller gauge catheters have generated increased interest in using smaller needles for both epidural and continuous spinal anesthesia. We report a case of a midshaft fracture of an 18-gauge Tuohy needle during an attempted administration of epidural anesthesia.

Case Report

A healthy 18-yr-old, 114-kg, 170-cm woman, gravida 2, para 1, at term was admitted to the labor suite in active labor. At 6–7-cm cervical dilatation, consent was obtained for epidural anesthesia. A CA-3 anesthesiology resident in the fourth month of an obstetric anesthesia subspecialty rotation attempted the block. The bony landmarks were difficult to palpate owing to obesity, so the patient was placed in the sitting position, and the skin was painted with an antiseptic solution and draped in the usual manner. The L3-4 interspace was approximated, and an 18-gauge, thin-walled Tuohy needle (American Medical Instruments, New Bedford, Mass.) was advanced until resistance was encountered. The stylet was removed, and a Pulsator syringe (Concord/Portex, Keene, N.H.) filled with 0.9% saline was attached. The needle was advanced with constant pressure on the syringe plunger. After inserting the needle an additional 1 cm, the resistance to advancement increased. The resident thought that this was due to calcified ligament, and the resistance was overcome with a transient increase in the pressure applied to the needle. The needle was then advanced to the hub with no perceived loss of resistance. On attempting to withdraw the needle, moderate resistance was encountered followed by a sudden release. The needle had fractured at the midshaft, leaving a 4.5-cm fragment in the patient. Epidural placement was abandoned. The patient was positioned on her side for the remainder of her labor and delivery without problems. After delivery, the patient was brought to the operating room, and the needle fragment was located by a neurosurgeon using fluoroscopy. The needle was lateral to the midline and had encountered the lamina of L4 rather than the interspinous ligament or the spinous process. Under local anesthesia, a small incision was made, and the fragment was grasped with a forceps and removed. Postoperatively, the patient complained of localized back pain with no radiation or signs of nerve injury.

We postulated that as the axial force on the needle against the bone increased, it bowed and eventually kinked. After this kink occurred, the resistance to forward movement decreased. This was misinterpreted as the "give" when a needle is passed over a vertebral spine, and the needle continued to bend as it was advanced to the hub. The action of withdrawing the needle caused it to break at the kink point. Our initial perception was that the needle involved in this incident might have been defective. However, studies of additional 18-gauge Tuohy needles from the same manufacturer revealed that they kinked easily when axial force was applied to the needle without the stylet in place. In view of this, we initiated a more systematic study of the stiffness and malleability of epidural needles to see whether there were differences among manufacturers.

Sample lots of ten 18- and 17-gauge epidural needles were obtained from seven manufacturers for comparison (Table 1). The outer diameter of each needle was measured at its midpoint using a micrometer. The needles were placed in a Luer lock fitting and compressed at a fixed rate of speed by an Instron Universal Testing Device (Instron Corporation, Canton, Mass.). This machine applies a variable axial force to the needle (Figure 1). Buckling force, the force applied when the needle first began to bend, was chosen as an index of needle stiffness. Malleability was assessed by measuring the distance (displacement) by which the needle was compressed in the axial direction when kinking first occurred. Descriptive statistics were obtained for each type of needle. To determine the association among selected variables, correlation coefficients were calculated. Comparisons among different groupings of needle types were made with nonparametric analysis of variance.

The outer diameters, buckling forces, and displacements for the different needles are displayed in Table 1. Each

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Table 1. Epidural Needle Measured Outer Diameters, Buckling Forces, and Displacements

Needle type[a]	Outer diameter (in.)	Buckling force (N)	Displacement (mm)
AMI (18)	0.0502 ± 0.000025	27.07 ± 0.38	15.34 ± 0.17
S (18)	0.0530 ± 0.000042	38.69 ± 0.57	16.60 ± 0.21
BN (18)	0.0532 ± 0.000025	40.32 ± 0.73	22.28 ± 0.25
M (18)	0.0499 ± 0.000017	28.58 ± 0.67	21.53 ± 0.24
K (18)	0.0502 ± 0.000035	29.49 ± 0.67	14.18 ± 0.11
BR (18)	0.0532 ± 0.000021	38.26 ± 0.76	16.64 ± 0.14
BD (18)	0.0498 ± 0.000032	30.56 ± 0.17	22.54 ± 0.33
BD (17)	0.0577 ± 0.000032	40.62 ± 0.38	24.37 ± 0.30
K (17)	0.0583 ± 0.000032	50.02 ± 0.43	18.90 ± 0.22
BN (17)	0.0589 ± 0.000063	57.49 ± 0.69	22.54 ± 0.18

AMI, American Medical Instruments, New Bedford, Mass.; BD, Becton Dickinson, Franklin Lakes, N.J.; BN, Burron Medical Inc., Bethlehem, Pa.; BR, Baxter International Inc., Deerfield, Ill.; K, Kendall Healthcare Products Company, Mansfield, Mass.; M, Manan Medical Products Inc., Northbrook, Ill.; S, Sherwood Medical Company, St. Louis, Mo.

Values are expressed as mean ± SEM; $n = 10$.

[a] Numbers in parentheses are gauges.

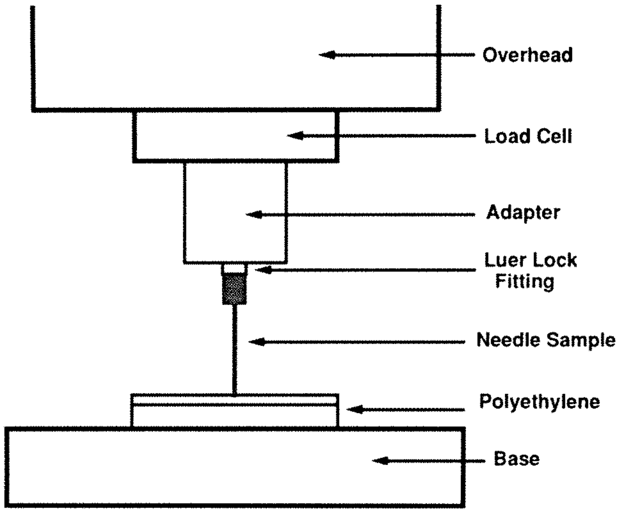

Figure 1. A schematic representation of the Instron Universal Testing Device.

entry in the table represents the mean of 10 samples with the standard error of the mean. The measured diameters stratified the needles into three different groups, as seen in Figure 2. The 17-gauge needles had an average diameter of 0.058 in. The 18-gauge needles fell into two distinct groups, with mean diameters of 0.053 and 0.050 in. Figure 2 also shows how the buckling force correlates with the measured outer diameter ($r = 0.93$; $P = 0.0001$). The three groupings of points differed significantly from each other with respect to buckling force ($P < 0.02$; Kruskal-Wallis nonparametric analysis of variance). Figure 3 shows the mean displacement plotted against the mean outer diameters for each brand of needle. Displacement did not correlate significantly with needle diameter ($r = 0.41$; $P = 0.24$). The Becton Dickinson, Burron, and Manan needles (Figure 3, solid dots) had displacement values significantly higher than the others ($P < 0.008$; Mann-Whitney U test).

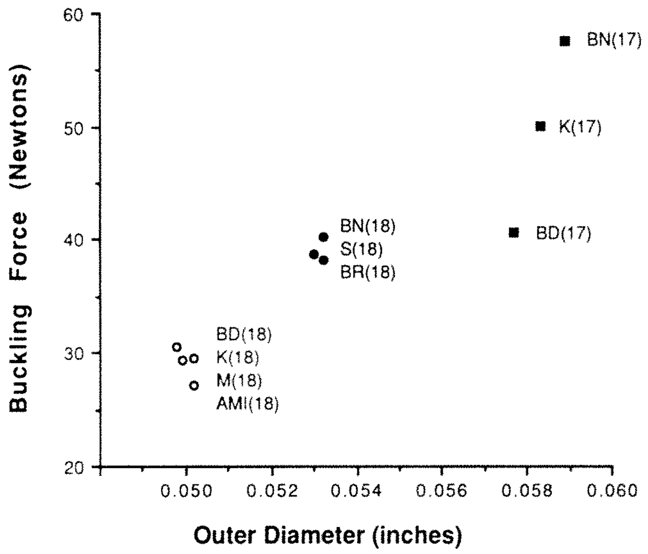

Figure 2. The needle buckling force (stiffness) plotted against measured needle outer diameter. Numbers in parentheses are gauges. Each buckling force and diameter measurement represents the mean of 10 samples. Abbreviations as in Table 1.

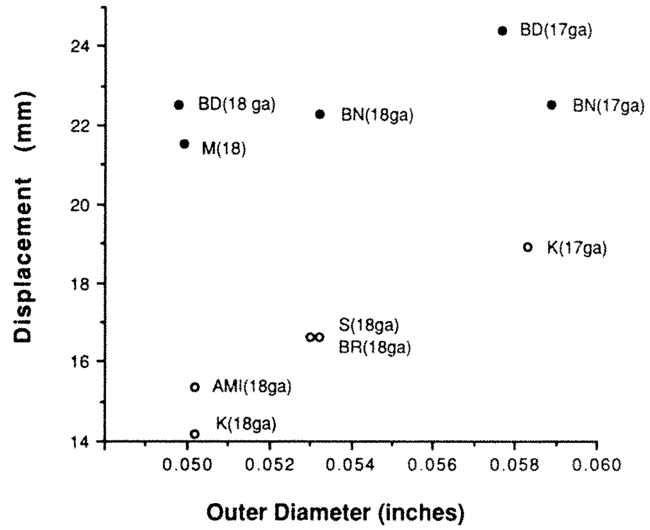

Figure 3. The distance the needle was compressed (displacement) plotted against the measured needle outer diameter. Each displacement measurement and diameter measurement represents the mean of 10 samples. ga, gauge. Other abbreviations as in Table 1.

Discussion

Epidural needles are often subjected to a substantial degree of axial force. This is due to the combination of the size and dullness of the needle, as well as the firmness of the interspinous ligaments and frequent impingement on bone. The standard procedure for placement of an epidural needle requires the removal of the stylet after the needle is advanced into the interspinous ligament. This allows the use of the loss of resistance or hanging drop technique to detect entry into the epidural space. With the stylet removed, the stiffness of the needle decreases, making it easier to buckle. After some critical amount of bending without the stylet in place, the shaft will kink, occluding the lumen. Once this kinking occurs, if the needle is then bent back toward its original shape, it is very likely to break. We cannot be certain that the fracture mechanism we propose, and partially verified in the laboratory, represents the events in our case. In vivo, the tissues surrounding the needle may apply forces in a nonaxial direction; if the patient should move, or if the needle is "walked off" the spinous process improperly, significant lateral or twisting forces may result.

Buckling force was proportional to the outer diameter of the needle, whereas displacement correlated poorly with diameter. Among needles of a given diameter, variations in displacement values probably arise from differences in the composition of the alloy from which the needle is constructed and from differences in wall thickness. We did not attempt to quantify these two variables.

In conclusion, we report a case of midshaft fracture of an 18-gauge epidural needle. As a result of this case, we studied epidural needles from seven manufacturers and found significant variation in their stiffness and malleability, as assessed by buckling force and displacement, respectively. The needle that failed in our case has the lowest buckling force and the second lowest displacement value of the needles we tested. This would suggest that this needle is more likely to bend than the others and will kink very soon after it begins to bend. Stiffness correlates with the measured needle diameter but malleability does not. Although midshaft fracture of an epidural needle occurs infrequently, this is a serious complication, because the retained needle fragment, being rigid and sharp, ought to be removed. The potential for further injury is obvious. If needle fractures indeed occur as we postulate, the needles that have the best combination of resistance to buckling and greater malleability once buckling occurs should be least likely to break.

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REVIEW ARTICLE

Extracorporeal Membrane Oxygenation

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Extracorporeal life support has evolved from a need for improved methods of gas exchange and cardiac support for patients with severe respiratory or cardiac failure, or both. Its development has been linked to that of cardiopulmonary bypass technology used in the operating room for cardiothoracic surgery. The first oxygenators to be widely used were bubble oxygenators, characterized by a direct blood-gas interface. Although effective, hemolysis limited the duration of safe exposure (1). The subsequent development of membrane oxygenators with a physical separation between the blood and gas phases minimized hemolysis and introduced the potential for long-term support (2). Membrane oxygenators are now used in many variations of extracorporeal life support, including venoarterial (VA) and venoveno (VV) extracorporeal membrane oxygenation (ECMO), extracorporeal carbon dioxide removal ($ECCO_2R$), and intravascular oxygenation (IVOX). This review will discuss all of these technologies but will focus primarily on the technique, history, and clinical indications for VA ECMO.

Venoarterial Extracorporeal Membrane Oxygenation

Venoarterial ECMO describes a circuit in which blood exits from the venous system, is oxygenated and ventilated, and is then returned to the arterial circulation (Figure 1). A drainage (venous) cannula is placed into the right atrium via the right internal jugular vein, which is distally ligated. Blood flows from the right atrium by gravity to a bladder and then onward to an occlusive blood pump. The bladder, with a volume of 30–50 mL, adds capacitance to the system, acts as a safeguard against inconsistent venous return, provides an access site for sampling and blood and drug administration, and "traps" any air entrained in the venous limb of the circuit. The occlusive, nonpulsatile blood pump is servoregulated to the pressure of the venous return. Venoarterial ECMO flows are usually directed to achieve approximately 100 $mL \cdot kg^{-1} \cdot min^{-1}$, that is, one-half to two-thirds of the patient's cardiac output. This flow, although usually adequate and easily achieved in neonates, is more problematic in adults. Venous drainage is the greatest limitation to ECMO flow, and, as such, it is important to cannulate the right atrium with the largest venous catheter possible (12–14F for neonates, 16–22F in children, and up to 28F in adults). After the pump, the blood enters the membrane oxygenator, which is a silicon envelope coiled around a spool and then encased in a plastic sleeve. The membranes are rated for gas transfer capability, which is a function of surface area: from 0.4 m^2 for a neonate to 3.5–4.5 m^2 for an adult. Fresh gas flows through the inside of the envelope while blood travels outside in a countercurrent direction. The sweep gas is responsible for delivering oxygen and washing out carbon dioxide; its composition and flow rate are adjusted in response to arterial blood gases; the usual fraction of inspired oxygen (FIO_2) ranges from 40% to 100%, with 1%–5% CO_2 added to maintain normocarbia. After the oxygenator, blood passes through a countercurrent heat exchanger and is then returned to the ascending aorta by way of a single end-hole catheter. At the time of cannulation, the arterial catheter is advanced through the right common carotid artery, which is ligated distal to the catheter.

There is a safety bridge connecting the proximal venous and distal arterial tubing, which is used to ensure continued circulation of blood through the membrane in the event that temporary discontinuation of ECMO is necessary. Normally occluded, the bridge can be opened while the catheters proximal to the patient are clamped, effectively separating the patient from the circuit.

Before cannulation, the circuit is primed with crystalloid and albumin, followed by heparinized blood corrected to normal pH and calcium concentration. The standard circuit volume, including the prime, is 500–650 mL in a neonate and as high as 2400 mL in the older child and adult. The patient and the circuit are

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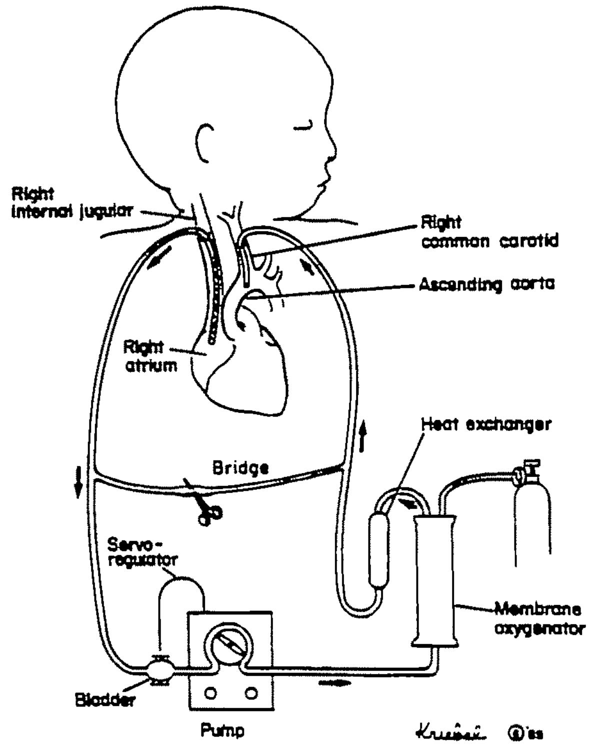

Figure 1. Diagram of the components of a venoarterial extracorporeal membrane oxygenation circuit.

then heparinized by a continuous infusion maintaining an activated clotting time of 200–240 s (1.5–2 times normal). This maintains a balance between catastrophic clot formation and bleeding complications.

While on VA ECMO, the native lungs participate little in gas exchange; therefore, the ventilator is set at "rest" settings. Although the more conventional settings would include room air, rate of 4 breaths/min with a peak inspiratory pressure of 20 cm H_2O, and positive end-expiratory pressure of 5 cm H_2O, some authors have reported improved native lung recovery with the use of higher positive end-expiratory pressures in the range of 12–14 cm H_2O (3). The ECMO flows maintained in any particular patient are chosen to support adequate gas exchange and mean arterial pressure. While on ECMO, the goal is Pao_2 60–100 mm Hg and $Paco_2$ 30–45 mm Hg. Hypocarbia is not routinely attempted.

The duration of ECMO support is a function of both the patient's rate of recovery from the underlying disease and from the frequent development of near complete opacification of the lung fields as seen by chest radiograph after the initiation of ECMO support. The etiology of this "whiteout" is poorly understood; however, it corresponds to a period of markedly decreased lung compliance during which time the patient's ability to exchange gas by way of the lungs is nearly impossible to support in the absence of ECMO (4,5). The decision to wean from ECMO is made when the lung compliance and radiographic image improve and the right-to-left shunt has decreased. The ECMO flow is slowly decreased while the patient's ability to support adequate gas exchange is tested. When the patient can demonstrate gas exchange with acceptable levels of conventional support, the ECMO catheters are removed, and routine conventional ventilatory support is continued.

Extracorporeal membrane oxygenation was first attempted in the early 1970s in a select population of adult patients with acute respiratory failure (ARF) refractory to conventional therapy (4,6,7). The first adult survivor was reported by Hill et al. in 1972 (8), and over the next 5 yr >150 adults were supported with ECMO with a reported survival rate of 10% (7). In response to these early reports, the National Institutes of Health sponsored a multicentered study to compare the effects of ECMO and conventional mechanical ventilation (CMV) in an adult population with terminal ARF. Ninety-six patients with an 80% predicted mortality were selected and randomized to CMV or ECMO. Unexpectedly, the results showed no difference in survival rates, with 8.7% survival with CMV and 9.3% survival rate with ECMO (6). Critics of this study claimed that the study entry criteria selected too heterogeneous a group of patients who, at the time they met study entry criteria, already had irreversible lung damage either from their primary disease or secondary to their ventilator management. They proposed that earlier institution of ECMO might have prevented pulmonary fibrosis, thus improving survival (4,7). The study also imposed a 5-day run limit on the use of ECMO in patients without clearly defined improvement. It is possible that this led to the premature termination of what might have proved to be an effective means of support. However, this study essentially halted the use of ECMO in adults with ARF. In retrospect, these results may not be applicable to the use of ECMO in the 1990s. During the period of the National Institutes of Health study, many patients were victims of an extremely virulent form of influenza virus with resultant pulmonary necrosis, limiting the possibility of reversible lung pathology. Also, compared to the newer, more efficient ECMO circuits, the circuits used during the 1970s captured much less of patients' cardiac output and relied much more on their lungs to achieve oxygenation and ventilation.

Neonatal Extracorporeal Membrane Oxygenation

A new population of neonatal patients with reversible lung disease have emerged as candidates for

ECMO. There are a number of obvious differences between potential adult and neonatal ECMO patients. Adults supported with ECMO often had ARF from destructive primary lung disease or from adult respiratory distress syndrome, which may result in severe parenchymal injury and fibrosis (9). In contrast, neonatal ARF is usually secondary to an abnormality of the pulmonary vasculature, immaturity of the surfactant system, or a chemical pneumonitis with small-airway obstruction, as in meconium aspiration (10). It is unusual for the neonate to have a primary destructive pulmonary process. This gives the neonate a higher likelihood of having reversible lung disease. Despite this advantage, the neonate, as well as the adult, is still subject to secondary lung damage from mechanical ventilation associated with barotrauma and elevated levels of inspired oxygen. Therefore, it would not only be important to select patients with reversible lung processes, but also to identify these patients early in the course of their disease and therapy before irreversible iatrogenic damage can occur. Fortunately, the usual natural history of neonatal respiratory failure makes it possible to identify infants with increased predicted mortality within the first few days of life, before major ventilator toxicity has occurred.

Each of these factors contributed to the success of neonatal ECMO. After a number of scattered case reports (11–15), in 1982 Bartlett et al. (16) published the first series of neonatal patients as a phase I study evaluating the safety and efficacy of ECMO support in infants. An experience of ECMO support in 45 infants during 1974–1982 was reported. The patient population was broad, with gestational ages of 27–44 wk and birth weights of 1–5.2 kg. The investigators tried to identify patients with a <10% chance of survival by devising a scoring system called the Neonatal Pulmonary Insufficiency Index in the first 24 h of life or by the attending neonatologist's clinical assessment that the patient was about to die with routine management. Patient diseases included respiratory distress syndrome, meconium aspiration syndrome (MAS), persistent fetal circulation, and sepsis. The overall survival was 50% and, by diagnosis, respiratory distress syndrome 43%, meconium aspiration syndrome 68%, persistent fetal circulation 60%, and sepsis 25%. Clearly the survival was considerably greater than the anticipated 10%, and the authors concluded that ECMO was effective and had improved outcome compared with conventional management.

As a result of cooperation among neonatal ECMO centers, the national experience has been continuously collected since 1981 in the national ECMO registry. This registry is sponsored by the Extracorporeal Life Support Organization and was created for the purpose of capturing the ECMO experience to track growth, success, or failure. Although patient reporting is voluntary, it is estimated that the registry captures at least 95% of the ECMO cases in the United States. However, because the registry includes different institutions, it reflects different degrees of local expertise with implementing and maintaining ECMO as well as different modes of conventional ventilatory support, and different criteria for predicting anticipated mortality. This results in a very heterogeneous population. In 1988, Toomasian et al. (17) reported the first formal review of the registry: 715 infants treated at 18 centers between 1980 and 1987 were included. These infants met their own institutional criteria for 80% predicted mortality. With ECMO support, 81% survived.

Table 1. Inclusion/Exclusion Criteria for Neonatal Extracorporeal Membrane Oxygenation

Inclusion criteria
1. 80% predicted mortality with conventional therapy
2. 34 wk completed gestation
3. Minimal weight 2 kg

Exclusion criteria
1. Sonographic evidence of significant massive intraventricular hemorrhage (>grade I)
2. Previous mechanical ventilation of >10 days
3. Hypoxemia secondary to congenital heart disease
4. Other anomalies precluding survival

Inclusion and exclusion criteria for neonatal ECMO have been formulated to include patients with a high predicted mortality and a reversible pulmonary process, and to exclude patients with a physiologic process that would not benefit from ECMO, or an underlying condition that would greatly increase the inherent risk of ECMO (Table 1). Specific entry criteria for neonates include an 80% predicted mortality, at least 34 wk completed gestation, and a minimal weight of 2 kg. The exclusion of infants <35 wk of gestation results from an early limited ECMO experience in which premature infants had massive intraventricular hemorrhages (IVH) (18,19). Neonates are also excluded if they have sonographic evidence of a significant IVH (4), with most ECMO centers accepting patients with grade I IVH (hemorrhage into the germinal matrix) and some centers accepting patients with IVH of grade II severity (extension of the hemorrhage into the ventricles). The inherent risk is that with systemic heparinization, the hemorrhage will increase in severity. Extracorporeal membrane oxygenation is not a cure for lung or heart disease; rather, it is a form of cardiopulmonary support while the patient's underlying pathophysiologic process abates. Therefore, infants are excluded if the hypoxemia is secondary to congenital heart disease or if they have other anomalies precluding reasonable survival. To identify these infants, all prospective ECMO candidates must first undergo a cardiac echocardiogram. In addition, to avoid supporting infants with preexisting ventilator damage, >10 days of previous mechanical ventilation is usually considered an exclusion criterion.

The greatest problem with patient selection has been the questionable validity of indicators of predicted mortality based on historical experience. The criteria presently used were formulated from retrospective chart reviews of infants with persistent pulmonary hypertension of the newborn (PPHN) (18,20–22). Most indicators use some measurement of oxygenation: alveolar-arterial oxygen difference, oxygenation index, and Pa_{O_2} (Appendix). Oxygenation index is the most commonly applied predictor, with an 80% predicted mortality identified by oxygenation indices ranging from 0.40 to 0.55 at various centers. It is important that every center determine what is most accurate at their own institution. Despite best efforts, historical control data provide a number of problems and inaccuracies. Historical data evaluate the care given during a prescribed time, and its relevance to current management is questionable. The use of historical controls has been criticized for potentially overestimating mortality. Cole et al. (23) reported that when retrospective ECMO criteria were prospectively applied to a neonatal population, the predicted 80% mortality was in reality only 23%, using only conventional mechanical ventilation. Dworetz et al. (24) from Yale reported a similar study and found only a 17% true mortality.

There have been two prospective randomized studies designed to overcome the limitations and criticisms of historical control populations and advances in CMV. The first by Bartlett et al. (25) compared ECMO with conventional management in patients with a predicted 80% mortality. The study design utilized play-the-winner randomization, which resulted in only 1 patient receiving CMV and 11 patients receiving ECMO. All the ECMO patients survived, but the conventionally treated patient died. This study was published in support of ECMO but was accompanied by much criticism (26). In a second study, O'Rourke et al. (27) again compared ECMO and conventional therapy. This study used an adaptive design; the first stage of 50:50 randomization was followed by a second stage with all patients receiving the "better" therapy. Initially, 10 patients were supported conventionally and 6 survived; whereas of the 10 patients receiving ECMO, all 10 survived. An additional 19 patients were supported with ECMO, with only one death. This study also supported ECMO, but like that of Bartlett, has been criticized for study design (28,29). Despite the limitation of patient selection and paucity of controlled studies, ECMO is now considered standard care for many full-term neonates with pulmonary diseases.

Table 2. Extracorporeal Life Support Organization Registry; Neonatal Entries as of October 1991

Disease	No. of patients	Survived (%)
MAS	2067	93
RDS/HMD	788	85
CHD	996	61
Pneumonia/sepsis	752	77
PPHN	692	88
Other	184	79
Total	5479	83

MAS, meconium aspiration syndrome; RDS, respiratory distress syndrome; HMD, hyaline membrane disease; CHD, congenital diaphragmatic hernia; PPHN, persistent pulmonary hypertension of the newborn.

Presently there are 5479 neonates enrolled in the registry, with an overall survival rate of 83% and a disease breakdown as shown in Table 2. What becomes clear from this is that survival is a function of primary diagnosis, with infants with meconium aspiration syndrome and PPHN experiencing a higher survival rate, and infants with congenital diaphragmatic hernia a much lower survival rate. Although ECMO "run times" are not standardized, some expected time frames do exist. The average run for all neonates is 5.5 ± 2.5 days, with meconium aspiration syndrome and PPHN usually lasting 5 days, neonatal sepsis 5–7 days, and congenital diaphragmatic hernia 7–14 days.

There are many interventions associated with ECMO that increase risk of morbidity. These include ligation and cannulation of the right common carotid artery and right internal jugular vein, systemic heparinization, exposure to blood products, being sick enough to meet entry criteria, and exposure to and possible failure of any of the component parts of the ECMO circuit.

The most frequent complication is bleeding. The most common sites of bleeding include the neck cannulation site, the central nervous system (CNS), and the tracheobronchial tree. Although systemic heparinization and alterations in normal platelet number and function are thought to be responsible for much of this observed bleeding, the etiology of CNS hemorrhage appears to be multifactorial. Possible additional factors include alteration of the normal arterial and venous cerebral circulations (30), the return of unfiltered blood to the systemic circulation, and systemic hypertension. Central nervous system hemorrhage is certainly the most problematic, with a reported 15% incidence in most centers (17,31). During ECMO, serial cranial ultrasound scans are obtained to detect CNS hemorrhage, and ECMO is discontinued in the presence of large or expanding hemorrhage.

Results from the ECMO registry disclose an 11%–30% incidence of CNS injury, leading to anything from subtle to devastating damage (32). Long-term neurologic follow-up of the ECMO survivors has been hindered by the young age of this population and the lack of a comparable control group. The results are limited to reports from several institutions. Towne et al. (33) published one of the first reports from the early ECMO experience at the University of California, Irvine. A 1–14-yr evaluation of 18 patients was reported: 13 (72%) had normal growth and development; 3 (17%) had moderate neurologic deficit; and 2 (11%) were severely injured. More recent clinical experience has been reported from Washington, D.C. (Children's National Medical Center), University of Virginia, and University of Michigan. The Children's National Medical Center studied 42 consecutive patients over a 2-yr period (31). The patients were evaluated with cranial ultrasound while on ECMO, computer tomography studies of the head before discharge, and neurodevelopmental tests and neurologic examinations at 1 yr of age. Despite the fact that 17 (41%) of the patients had abnormal radiographic findings by cranial ultrasound and computed tomography, only 9 (21%) of the children were delayed, 8 (20%) had suspect examinations but were not delayed, and the remaining 25 (59%) patients had normal neurologic examinations. Krummel et al. (34) evaluated six patients and reported five (83%) normal 1–3 yr after ECMO. Andrews et al. (35) reported the follow-up of their first 14 survivors: 9 (64%) had normal motor development; 10 (71%) had normal mental ability. Two more recent studies have interpreted their data by comparison with previously reported morbidity statistics among neonates with severe respiratory failure treated with conventional therapy (36,37). Essentially, they reported no statistical differences between the developmental outcome of ECMO survivors and conventionally treated neonates.

Renal complications also occur commonly during ECMO. The development of renal failure, thought to be suggestive of the development of either pre- or intra-ECMO multisystem organ failure, carries a predicted mortality of >80% shown in one study (38). Hypertension, manifested as systolic pressure >100 mm Hg while on ECMO, is another commonly observed phenomenon, with an incidence as high as 58% in one study (39). The occurrence of hypertension does not correlate with plasma renin levels, colloid volume infused, or milliequivalents of sodium delivered. Possible etiologies include an increase in cardiac stroke volume, preexisting myocardial damage in the nonhypertensive patients, or an alteration in the patient's ability to handle sodium or water.

To circumvent the complications associated with carotid ligation, some centers are attempting carotid artery reconstruction. A recent study, published in 1991, utilized noninvasive magnetic resonance imaging and ultrasound to demonstrate patency of the right common carotid artery in 14 of 18 infants undergoing reconstruction (40). Infants were considered ineligible for this procedure if they demonstrated neurologic abnormalities before decannulation or if they had undergone reexploration for excessive bleeding at the cannulation site. Six-month follow-up was obtained in only seven of the infants; however, the patency rate was 100%.

The registry review (17) also pointed out the importance of the institution's previous experience with ECMO. The patient data were analyzed to see whether outcome improved with technologic experience. Survival of the first 10 patients at all centers was 73.5%, compared with 83.7% if the first 10 patients were excluded. This difference could not be explained by any differences in pre-ECMO characteristics of these patients. Of note, the first 10 patients had a higher incidence of complications (2.26 per patient) compared with later patients (1.6 per patient).

The current status of neonatal ECMO can best be described as controversial and changing. The national experience has steadily grown over the past years. The results of that experience suggest a very high survival rate, and short- and long-term follow-up studies suggest a tolerable morbidity. However, like so many therapies aimed at critically ill patients, ECMO has not undergone the rigors of a large conventional, prospective, randomized study to prove or disprove efficacy. What makes this increasingly difficult is that as ECMO technology has improved, so has CMV, and perhaps these improvements may diminish the disparity in patient outcome from these two methods of support.

The main change in CMV is a progression toward "gentle," less aggressive ventilator support. The mainstay of conventional management of PPHN has been to maximize pulmonary vasodilation by maintaining relative hyperoxia and inducing both a respiratory and metabolic alkalosis (41,42). However, this approach exposes the infant's lungs to 100% oxygen and often markedly elevated airway pressures. Some clinical investigators believe that not only does this approach inflict significant damage to the lungs, but that there is no clearly proved benefit (43,44). These clinicians suggest the use of low airway pressures and F_{IO_2} to maintain just adequate arterial blood gases: Pa_{O_2} 50–60 mm Hg and Pa_{CO_2} <60 mm Hg. Wung et al. (45) from Columbia University have been one of the proponents of this "gentle" therapy. In

1985, they reported 90% survival without the use of ECMO in term neonates with severe respiratory failure. In addition, they also suggest that their method of ventilation results in a much lower incidence of bronchopulmonary dysplasia. Proponents of ECMO state that the risk of residual lung disease in ECMO patients (0%–8%) compares favorably with those treated with conventional mechanical therapy (up to 35%), and some individuals speculate that earlier ECMO intervention may help to eliminate chronic lung disease altogether (18,35,46). These reports do demonstrate dramatically the institutional and chronologic heterogeneity of CMV and the potential problems in utilizing ECMO criteria developed in one institution at a fixed time.

Pediatric Extracorporeal Membrane Oxygenation

As the technology for neonatal ECMO became routine in many pediatric centers, ECMO was soon applied to older children who were thought to be at risk for dying of pulmonary disease. In most situations, it has been offered as a "last resort" or rescue therapy on an individual case basis (8,47–51).

The existing experience of pediatric ECMO for ARF is documented in several small clinical reports and in the Extracorporeal Life Support Organization registry (48,50,52). As of October 1991, 285 pediatric patients have been reported in the registry. There are no specific entry criteria for pediatric ECMO. Typically, ECMO is reserved for those patients with an anticipated 100% mortality, as judged by their physician. The heterogeneity of patient age, development, and etiology of disease makes it even more difficult to define this population compared with neonates.

In the older child, ARF is caused by a number of diseases, which, although different, may share some common pulmonary pathophysiology. Unlike the neonate with PPHN, many of the acute respiratory diseases in children are associated with direct air-space injury, with necrotizing alveolitis, and with deposition of fibrin (53,54). In addition, most older children are exposed to longer periods of ventilatory support before meeting criteria for CMV failure. As a result, the older child has a much higher probability of iatrogenic injury from elevated airway pressure and oxygen exposure. In addition, while most lung diseases share a final common pathophysiology, the inciting event can be remarkably different. It is not clear that ARF from hydrocarbon ingestion is the same as ARF from viral pneumonia or near drowning. Also, because pediatric patients represent a wide spectrum of ages, and because the child's lungs continue to grow, mature, and remodel during the first years of life, one wonders whether equivalent injuries have the same morbidity and mortality in a child aged 10 mo compared with one aged 10 yr.

The natural history of ARF in older children is poorly understood. Specifically, is death caused by inadequate gas exchange? Studies of adult patients with ARDS show that <20% of these patients die of respiratory failure (55,56). The majority die of multisystem organ failure, and mortality is particularly elevated in the presence of sepsis or malignancy, or both. Similar studies in pediatric patients are scant, but the existing evidence supports the same findings (57–59). This is in sharp contrast to the neonate with PPHN who often succumbs to hypoxemia. Therefore, in the older child can maintenance of gas exchange change the natural course of the disease? Should ECMO be offered earlier before multisystem organ failure occurs, or should it be a contraindication for ECMO?

To date, most pediatric ECMO has used the same technologic approach as routine neonatal VA ECMO, with cannulation of the right internal jugular vein and the right common carotid artery. The risks of ECMO in the older patient are similar to those in the neonate. Although there is anecdotal evidence that the older child has more hemorrhagic complications with pulmonary and cannulation site bleeding, there appear to be fewer CNS hemorrhagic complications (60).

Cardiac Extracorporeal Membrane Oxygenation

Venoarterial ECMO has also been used to support cardiac function in pediatric patients with cardiovascular dysfunction. The majority of these patients are children who develop low cardiac output syndrome or severe pulmonary artery reactivity, or both, after surgical repair of congenital heart defects. There are also a few children who have been placed on ECMO preoperatively, and others with myocarditis or cardiomyopathy in whom ECMO has provided a bridge to cardiac transplant or hemodynamic support until their myocardial function resolves.

As of the end of 1991, 494 children have been supported with ECMO for acute cardiovascular failure. The majority (90%) of these patients were placed on ECMO after surgical repair of congenital heart disease; the remainder had cardiac failure from myocarditis or a cardiomyopathy (52). The overall survival rate is reported to be 47%. A few patient series have been reported (61–65), and a number of patterns have emerged. The average duration of ECMO support in these patients was much shorter than for ARF patients. Pennington et al. (66) reported an average

ECMO duration of <4 days in survivors and noted that those requiring >7 days subsequently died. Another observation was that survival correlated with the time of ECMO initiation; patients who required ECMO support either in the operating room or within the first six postoperative hours experienced a high mortality of >90%, whereas those who demonstrated more perioperative stability and were placed on ECMO at >4 h had an improved outcome. This dramatic difference may represent the fact that the group requiring early ECMO intervention had greater myocardial damage or that they suffered more hemorrhagic complications, or both, as a result of the resumption of systemic heparinization before adequate hemostasis.

The indications for ECMO as postoperative support are poorly defined. Similar to the pediatric ARF population, there have been no retrospective or prospective controlled studies. The heterogeneity of the population makes it difficult to identify predictors of mortality. Most clinicians select ECMO candidates on the basis of evidence of decreased end-organ perfusion and the failure of pharmacologic support of the circulation. Dosage of inotropic agents, elevation of right or left atrial pressures, decreased mixed venous oxygen saturation, metabolic acidosis, decreased urine output, and increased serum levels of liver enzymes are all factors used to select patients. Investigators have reviewed their experience with selected groups of patients to predict mortality and to guide patient selection for ECMO. As an example, Klein et al. (65) reported in a retrospective chart review that there was a <3% survival in postoperative cardiac patients, who at 8 h after bypass required >10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of dopamine and had <2.0 $mL \cdot kg^{-1} \cdot h^{-1}$ urine output. Obviously, these findings vary with the types of cardiac diseases studied, the preoperative status of the patients, the surgical repair, and the institutional approach to inotropic management. These results must be evaluated independently in each institution, and regardless of the indicators used, it is important to identify these ECMO candidates before the development of irreversible end-organ failure and cardiac arrest. Two clear prerequisites for postoperative ECMO include a successful surgical repair and cardiac anatomy compatible with ECMO cannulation. Contraindications for postoperative ECMO include irreversible neurologic damage and active uncontrolled bleeding at the surgical site.

The ECMO procedure in acute cardiovascular failure is similar to VA ECMO used for ARF. The flow rates required to support perfusion are often greater: 100–200 $mL \cdot kg^{-1} \cdot min^{-1}$. This emphasizes the need for very large venous catheters. Transthoracic cannulation is often used to allow larger catheters; however, the main disadvantage of this is the difficulty in assessing and treating cannula site bleeding.

During ECMO, the blood returning at high flow rates to the ascending aorta can increase left ventricular afterload. This can have a negative impact on those patients with left or biventricular failure. Decompression of the left side of the heart can be achieved through placement of a left atrial or left ventricular catheter (65,66). Although this may help unload the left ventricle, it is obviously more invasive and provides added risks.

Other forms of extracorporeal oxygenation and support have evolved from the original techniques and applications of VA ECMO. These include VV ECMO, $ECCO_2R$, and IVOX.

Venoveno Extracorporeal Membrane Oxygenation

In VV ECMO, blood is drained from the right side and returned to the right side of the circulation. This can be accomplished with either a single- or double-catheter system. In the double-catheter system, one catheter is used for drainage and the other for return (67,68). Most commonly, outflow is through a right atrial catheter, and blood is returned to the femoral vein (68). Unfortunately, with this system there is recirculation when some of the oxygenated blood returned via the femoral vein is captured by the outflow catheter in the right atrium and is recirculated through the ECMO circuit.

Various types of single-catheter VV ECMO have been attempted. The most promising is a double-lumen catheter that allows continual outflow through the proximal port and inflow through the distal port (69). Despite the two ports, there is some recirculation of oxygenated blood. Another single-catheter system uses a single-lumen catheter. Similar to dialysis systems, there are separate infusion and outflow times that are controlled by a tidal flow system (70,71).

Regardless of which system is used, VV ECMO has some basic differences compared with VA ECMO. Perhaps most important is the fact that VV ECMO does not support cardiovascular function. Second, the patient's Pa_{O_2} is lower in VV ECMO than in VA ECMO; this reflects the fact that there is some degree of recirculation of oxygenated blood back into the ECMO circuit. Because the efficiency of gas exchange is less than in VA ECMO, often the patient's lungs have to be used to augment oxygenation. This obviates the ability to totally rest the lungs, which may cause further lung injury and impact the ability of the patient's lungs to heal. Despite these differences, many centers are now involved in neonatal VV ECMO, and in some institutions it is the treatment of choice over VA ECMO.

Extracorporeal CO_2 Removal

Another approach to extracorporeal gas exchange is extracorporeal CO_2 removal ($ECCO_2R$). This mode of support dissociates oxygenation and carbon dioxide elimination into essentially two separate functions. The lungs are used for oxygenation, and the ECMO circuit maintains ventilation or removal of carbon dioxide. Because the circuit only supports ventilation, a relatively small fraction of the cardiac output is obligated to go through the ECMO circuit. This can be accomplished by using VV ECMO, either with a single catheter placed in the internal jugular system or via a two-catheter system, using a combination of the jugular-to-femoral or femoral-to-femoral systems. Oxygenation is then supported by the lungs. Low-frequency positive pressure ventilation is used and incorrectly called "apneic oxygenation." In the described series, a catheter delivers low-flow 100% oxygen at the level of the carina, while the ventilator delivers 4–12 breaths/min with peak pressures of 40–50 cm H_2O and peak end-expiratory pressures of 8–15 cm H_2O. While the patient is on this support, systemic heparinization is required (72).

The advantage of this system, as well as VV ECMO, over more routine VA ECMO is the fact that the arterial system does not need to be accessed. This is particularly important in consideration of the fact that the standard arterial approach involves cannulation and ligation of the common carotid artery in the infant and child.

$ECCO_2R$ requires the patient's lungs for oxygenation. This implies that $ECCO_2R$ should be instituted before impairment of gas exchange is too severe. If the lungs cannot support any oxygenation, $ECCO_2R$ is not an option.

In 1986, Gattinoni et al. (72) reported the results of $ECCO_2R$ in 43 patients who, in their estimation, had an expected mortality of >90% with conventional therapy. These patients were placed on $ECCO_2R$ as rescue therapy. Thirty-one (72.8%) showed improvement in lung function, and 21 (48.8%) survived. Although this was an uncontrolled study, it was stated that $ECCO_2R$ was a safe and effective method to support gas exchange and that it should be considered as an alternative to standard methods of mechanical ventilation (72).

Intravascular Oxygenation

A new investigational method of gas exchange is the intracorporeal intravenous mechanical gas exchange system, which has been referred to by the acronym IVOX. The concept is simple: a small-diameter holofiber membrane oxygenator is placed into the inferior vena cava, thereby obviating the need for an extracorporeal circuit. The oxygenator is introduced via a sheath placed through a common femoral venotomy. The oxygenator is advanced in a cephalad direction with the distal tip lying in the superior vena cava or the right atrial appendage. Once inserted, the oxygenator unfurls, exposing the expanded surface area necessary for gas exchange. The oxygenator has a double-lumen gas transport tube that allows for an inflow and outflow limb. Oxygen passes through the inflow limb, driven either by positive pressure or by suction, and provides oxygenation and washes out carbon dioxide. The oxygenators are made in three different sizes, with surface areas that range from 225 to >9000 cm^2 with external diameters of 1.8–10.8 mm. Gas exchange is a function of the oxygenator surface, the sweep gas through the oxygenator, the mixed venous Po_2 and Pco_2, and the patient's cardiac output. The oxygenator surface in IVOX cannot entirely support gas exchange, and similar to $ECCO_2R$, the patient's lungs must be used (73,74).

The IVOX system has successfully supported gas exchange in 20–40-kg dogs and 60-kg sheep. There have been no reportable complications. There was little or no hemodynamic effect on central venous pressure or cardiac output after insertion. There has been no evidence of gas emboli or bubbling; and, finally, neither clotting nor thrombi deposition was observed in any of these animals. Of note, all animals were fully heparinized.

Under surveillance of the Food and Drug Administration, clinical trials are in progress to test the efficacy of IVOX in adults. In the phase II trial, IVOX is being offered to patients with at least a 90% predicted mortality from continued conventional methods of support (75).

Summary

Extracorporeal membrane oxygenation is still a relatively new technology that has recently achieved recognition after initial clinical disappointment in the late 1970s. At present, it is considered standard therapy for the full-term infant with PPHN who fails CMV and extraordinary, heroic therapy for older children and adults with ARF or cardiac failure, or both. Currently, the emphasis is on developing new technologies for increasing safety and effectiveness. Areas of interest include heparinless circuits, carotid artery reconstruction, improved monitoring, and expanding applications of VV ECMO. As ECMO becomes safer and more effective, it is believed that new and expanding patient populations will emerge to include premature infants, earlier intervention in term infants, and more liberal application to pediatric and adult populations.

Appendix

1. Oxygenation index (OI):

$$\mathrm{OI} = \frac{(\mathrm{MAP})(\mathrm{FIO_2})(100)}{\text{Postductal } \mathrm{PaO_2}},$$

where MAP = mean alveolar pressure; $\mathrm{FIO_2}$, fraction of inspired O_2; and $\mathrm{PaO_2}$ = arterial oxygen tension.

2. Alveolar/arterial oxygen difference ($\mathrm{AaDO_2}$):

$$\mathrm{AaDO_2} = \mathrm{PAO_2} - \mathrm{PaO_2},$$

where $\mathrm{PAO_2}$ = alveolar oxygen tension = $[\mathrm{FIO_2} \times (\mathrm{P_B} - \mathrm{P_{H_2O}})] - \mathrm{PaCO_2}/R$, and $\mathrm{P_B}$ = barometric pressure; $\mathrm{P_{H_2O}}$ = water vapor pressure; $\mathrm{PaCO_2}$ = arterial CO_2 tension; and R = respiratory quotient difference.

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LABORATORY REPORT

Local Anesthetic-Sensitive Electrodes: Preparation of Coated-Wire Electrodes and Their Basic Properties In Vitro

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Coated-wire electrodes with local anesthetic (LA) cation-selective membranes were prepared, and their properties in vitro were investigated. Copper wires (0.8-mm diameter) were coated with gel membranes of 110 mg of poly(vinyl chloride), 5 mg of ion pairs of tetraphenylborate anion with LA cation, 100 mg of dioctylphtalate, and 1.5 mL of tetrahydrofuran. This was the composition determined to be most suitable. Their electromotive force relative to an Ag/AgCl electrode was measured in LA solutions. The lidocaine, dibucaine, and mepivacaine electrodes all showed good Nernstian response at 25°C in aqueous solutions in the concentration ranges of 1×10^{-4} to 1×10^{-2} mol/L, 4×10^{-5} to 1×10^{-2} mol/L, and 5×10^{-5} to 1×10^{-2} mol/L, respectively. The response time was within 10 s. The electrode potential decreased as the pH in the solution increased, with a corresponding decrease of the protonated form of LA. The hydrophobic nature of the LA was closely related to the electromotive force and to the selectivity of the electrode toward various LA cations. Dibucaine, the most hydrophobic, had the highest electrode potential. The more hydrophobic the LA of the electrode, the less it is interfered with by other LA molecules. The more hydrophobic the interferent cation, the more it acts on the electrode potential. The electrode system could also measure LA in human plasma at 37°C, although the responsiveness was depressed in the low concentration range owing to binding of LA to the serum protein. Its small size, convenience of handling, good response, and simplicity of measurement indicate the feasibility of the electrode system for in vivo application.

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The concentration of local anesthetics in plasma, like that of many other drugs, is usually assayed by high-performance liquid chromatography, gas chromatography, radioimmunoassay, or fluorescence polarization immunoassay. These methods require special techniques and equipment and are expensive for routine use. They also require the sampling of a certain amount of blood. As a result, it is difficult to discern the detailed pharmacokinetics concerning the effects or intoxication of local anesthetics. We have developed coated-wire electrodes sensitive to local anesthetic cations that are small and feasible for future use in vivo. This report describes the basic principle of the sensor system, preparation, and some properties of the electrodes in vitro.

Principle

Local anesthetics used clinically are basically tertiar amine compounds. Most of the molecules exist in protonated form (cation) in vivo, according to th Henderson-Hasselbalch equation. In general, the a tivity (which is nearly equal to "concentration" i dilute solutions) of a cation or anion can be dete mined electrochemically. When two solutions wit different concentrations of an ion are separated by certain ion-selective membrane, ions keep movin through it until equilibrium is attained, where th chemical diffusion force balances the electromotiv force. This is just the basic concentration cell. Th Nernst equation shows that the ratio of the io activity of both solutions corresponds to the electr potential difference between them; pH/mV meters i general use are based on this principle. The mai problem with this method is how to make the men brane selective only to the particular ion concerned

Local anesthetics are amphiphilic. The amine en is hydrophilic and can be positively charged, wherea the aromatic end is greatly hydrophobic. If a catior

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exchange membrane (e.g., poly(vinyl chloride) [PVC] membrane) incorporates a certain kind of local anesthetic cation with some hydrophobic anions as ion carriers, the hydrophobic nature enables this membrane to react only to the local anesthetic cations concerned in the surrounding solution.

Thus, a local anesthetic cation-selective electrode can be obtained that consists of this ion-selective membrane and an inner solution of a known concentration of the local anesthetic. When this electrode is immersed in an ionic solution of unknown concentration (the outer solution), the ratio of the two concentrations can be calculated from the electromotive force between the inner and outer solutions.

This type of sensor is easily made, and its use in potentiometry exhibits good response; however, it is still too large to insert into blood vessels for the purpose of in vivo investigations.

We developed another type of electrode: a coated-wire electrode that operates as described earlier. This sensor simply consists of a copper wire coated with the membrane described previously and has no inner solution. The details of the mechanism by which the activity of local anesthetic cations surrounding the sensor membrane is converted to the electric potential of the wire are still unknown. However, this simple sensor also works in accordance with the Nernst equation (Appendix 1) (1). Because it needs no inner solution and can be miniaturized, it may be applicable to in vivo use.

In the following, we report the preparation of the coated-wire electrodes sensitive to some amide-type local anesthetics: lidocaine electrodes, dibucaine electrodes, and mepivacaine electrodes, and their basic properties for potentiometric analysis in vitro.

Methods

Construction of Electrodes

The coated-wire electrodes were prepared by the same method described previously (2). As shown schematically in Figure 1, copper wires (0.8 mm diameter) were coated to a thickness of about 0.4 mm with membranes of PVC matrix that included the ion pairs, dioctylphtalate (DOP), and tetrahydrofuran (THF) in various compositions.

A high-molecular-weight PVC (Wako, Japan) was used. To make the ion exchangers of the membrane, local anesthetic–tetraphenylborate ion pairs were prepared from hydrochlorides of local anesthetics and sodium tetraphenylborate (NaTPB) (Aldrich) according to the same method described previously (2) for other ion pairs. Hydrochlorides of local anesthetics used were purchased from Sigma Chemical Co. (St. Louis, Mo.), except for lidocaine/HCl (Fujisawa Yakuhin, Japan). Dioctylphtalate (Tokyo Kasei, Japan) was used to plasticize the PVC membrane. Tetrahydrofuran (Wako, Japan) was used as a common solvent for the ion pair, DOP, and PVC.

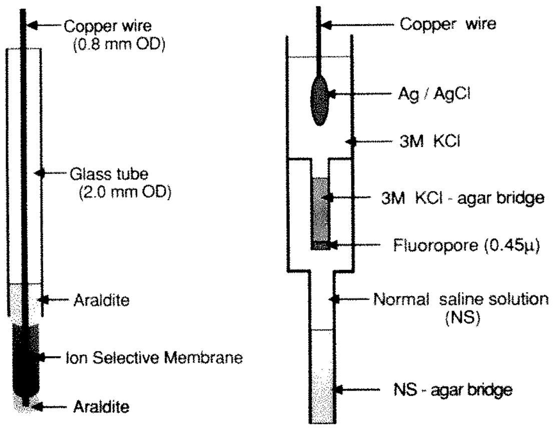

Figure 1. The structure of the coated-wire electrode (**left**) and the reference electrode (**right**).

Glass and epoxy resin (Araldite) covered the surface of the wires to maintain isolation, except for the membrane portion. The electrodes were allowed to stand for at least 10 h in contact with air, and afterward were stored by immersion in 10^{-3} mol/L solutions of the local anesthetics for which they were selective.

Potential Measurement

The coated-wire electrodes were used as the indicator electrodes, whereas an Ag/AgCl electrode connecting a normal saline agar bridge was the reference electrode (Figure 1). Immersing both the electrodes in test solutions (i.e., local anesthetics to which the electrode was selective in 0.15 M, pH 7 phosphate buffer), we recorded the electromotive force. The electrochemical system was as follows: local anesthetic coated-wire electrode/test solution/normal saline agar bridge/3 mol/L KCl solution/Ag/AgCl electrode. The electromotive force was measured with a multi-ion monitor (Yamashita Giken, Tokushima, Japan) at 25°C in the constantly stirred solution. A circulating water bath controlled the temperature of the test solution. To construct calibration curves (electromotive force vs concentration), suitable increments of local anesthetic solution were added so as to cover the concentration range 10^{-6} to 10^{-2} mol/L.

We prepared five coated-wire electrodes, each with 8 to 13 types of membrane compositions. We investigated the effect of membrane composition on the responsiveness, stability, and reproducibility of the electrode potential and determined the suitability of the composition according to these points. Using the electrodes with the most suitable composition, we performed the following tests.

pH change of the solution. We examined the effect of pH of the test solution on the electrode potential for 10^{-4} mol/L solutions of local anesthetics in normal saline at 25°C. The pH was changed repeatedly in the range 4–11 by the addition of 10^{-1} mol/L hydrochloric acid or sodium hydroxide solutions, or both, containing 10^{-4} mol/L of the corresponding local anesthetic.

Selectivity of the electrodes. The influence of other local anesthetic cations toward each electrode potential was investigated. Selectivity coefficients (Appendix 2) were determined by the separate solution method (3,4) using 10^{-2} mol/L of local anesthetic solutions.

Response in plasma. The response of the electrodes in human plasma was also examined to ascertain the feasibility of their use in vivo. Sensitivity, stability, and reproducibility of the electrode potential were checked at 37°C in constantly stirred Plasmanate (Miles Inc.) with the same electrode system.

Results

Composition of Electrode Membrane

The best results were obtained with an electrode with a membrane prepared from mixtures of 100 mg of DOP, 110 mg of PVC, and 1.5 mL of THF for all local anesthetic ion-selective membranes. As for ion pairs, the potential response curves shifted in a parallel manner to the negative side as the membrane content of the local anesthetic–TPB ion pairs increased. However, the slope of the linear part of the curve did not change when the range of the ion pair content was within 1–25, 1–10, and 1–25 mg for lidocaine, mepivacaine, and dibucaine, respectively, the mixtures DOP, PVC, and THF being held constant as above. When the contents of DOP (<50 mg) and ion pair (<1 mg) decreased, the electrode potential became unstable owing to the increased resistance of the membrane. A large excess of DOP and ion pair in the membrane caused the surface of the copper wire to gradually become black, shortening the electrode lifetime and decreasing the slope of the potential curve. We adopted 5 mg of the local anesthetic–TPB ion pairs for all the electrode membranes to standardize the quality of electrodes and to evaluate the potential differences between electrodes of various local anesthetics.

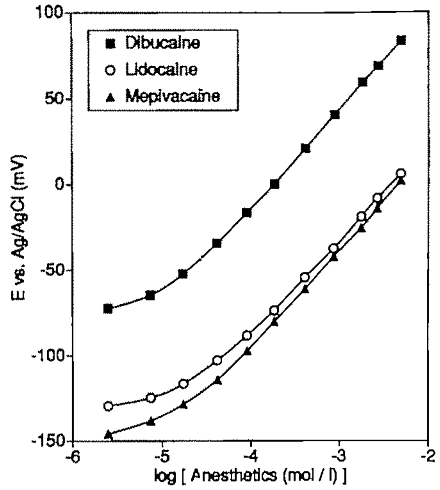

Figure 2. Relationship between the local anesthetic concentration in phosphate-buffered solution and the electrode potential relative to the Ag/AgCl electrode at 25°C.

Response of the Electrodes

The typical calibration curves of each electrode with this composition are shown in Figure 2. The linear response range of the calibration curves, their Nernstian slope, and the coefficients of variation of the slopes are shown in Table 1. The potential changes of the lower concentration range compared with the linear response range are also shown in Table 1.

The response time was within 5–10 s for all of the electrodes in the local anesthetic concentration range 10^{-5} to 10^{-2} mol/L and 30 s in 10^{-6} mol/L. Figure 3 shows a typical response curve. Reproducibility of electrode potential was checked by increasing or decreasing the concentration. Fluctuations of the electrode potentials were within 1% of the coefficient of variation when the concentration was changed from 10^{-4} to 10^{-2} mol/L or from 10^{-2} to 10^{-4} mol/L. Although continuous measurements of the electrode potential were taken over an 8-h period, the change in the electrode potential remained within 3 mV in this concentration range. We confirmed that the electrode could be repeatedly used to determine the local anesthetic concentration every day for 30 days.

Effect of pH

Figure 4 shows the potential variation versus pH change in one of the five electrodes of each local anesthetic electrode prepared. All of the other electrodes for the same local anesthetic showed a similar curve.

Table 1. Potential Characteristics of the Electrodes

Electrode	Linear response range Concentration (mol/L)	Slope (mV/decade)	CV (n = 5) (%)	Lower concentration range Potential difference[a] (mV/decade)	CV (n = 5) (%)
Lidocaine	1×10^{-4} to 1×10^{-2}	55.9	0.9	21.5	2.3
Mepivacaine	5×10^{-5} to 1×10^{-2}	56.8	0.6	25.0	1.3
Dibucaine	4×10^{-5} to 1×10^{-2}	58.6	0.3	31.0	0.5

CV, coefficient of variation.

[a] Differences in the electrode potentials between $10^{-5.5}$ M and $10^{-4.5}$ M of the local anesthetics.

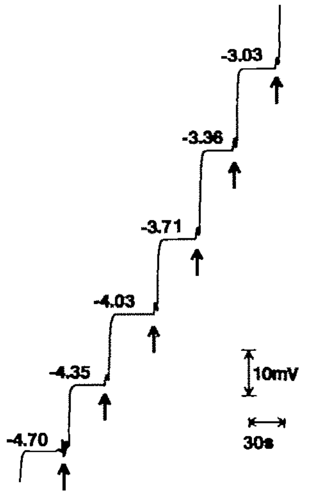

Figure 3. Continuous recording of the potential response of the lidocaine electrode with successive additions of lidocaine to the test solution. *Arrows* indicate the points at which lidocaine was added. *Small spikes* in the curve are the noise due to adding lidocaine with a microsyringe. *Values* on the curve represent the lidocaine concentration ($\log_{10}$ of mol/L) of the test solution.

Selectivity of the Electrodes

Results are summarized in Table 2. Value of selectivity coefficients means that the smaller the value of the interferent ion, the less the ion can interfere with the electrode potential. The dibucaine electrode was the least affected by the presence of other local anesthetics.

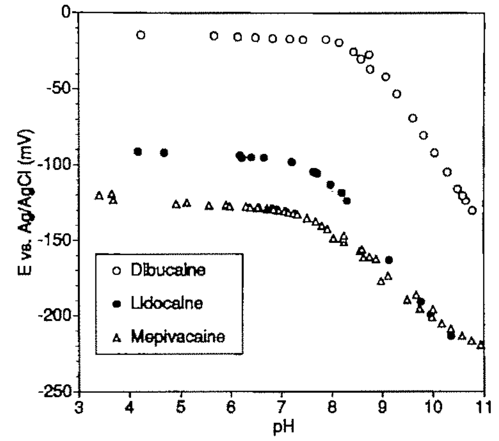

Figure 4. Effect of pH on the response of the local anesthetic electrodes.

Table 2. Selectivity of Electrodes Toward Other Local Anesthetics[a]

Interferent	Electrode Mepivacaine	Lidocaine	Dibucaine
Benzocaine	−1.26	−1.79	−3.40
Procaine	−0.17	−0.85	−2.59
Mepivacaine	—	0.05	−1.99
Lidocaine	0.05	—	−2.09
Tetracaine	1.10	1.05	−0.92
Bupivacaine	1.50	1.30	−0.78
Dibucaine	1.74	1.97	—

[a] Values are expressed as $\log_{10}$ of selectivity coefficients of the interferent to the electrode cation.

Electrode Response in Plasma

The typical calibration curves of each electrode are shown in Figure 5. The general potential level in the plasma showed some displacement from that in the crystalloid solution. The response curve was less linear than that in the crystalloid solution, and the potential difference versus concentration change of the curve was smaller, especially in the low-concentration range of the local anesthetic (Table 3). The response time was within 10–20 s for all of the electrodes in the concentration range 10^{-5} to 10^{-3} mol/L and 30 s at 10^{-2} mol/L. Reproducibility of electrode potential was checked by increasing or decreasing the concentration. Fluctuations in electrode potentials are also shown in Table 3. Electrode potential change over 4 h of continuous measurement was within 3 mV in the concentration range 10^{-4} to 10^{-2} mol/L. After measurement in Plasmanate, we checked the calibration curve of the electrodes in the crystalloid solution again and found no deterioration in the response.

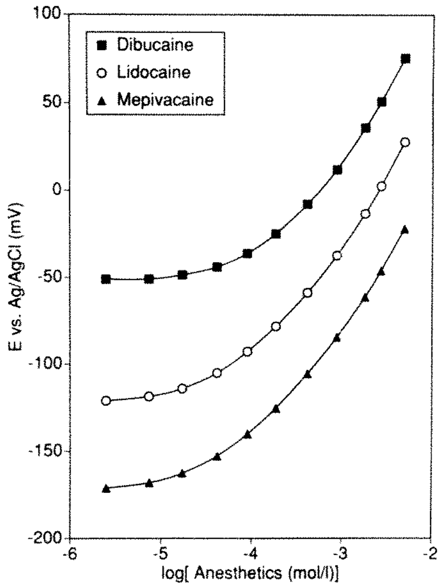

Figure 5. Relationship between local anesthetic concentration in Plasmanate and the electrode potential relative to the Ag/AgCl electrode at 37°C.

Discussion

The measurement of drug concentrations in the body usually involves the removal of some blood or body fluid, which prevents the evaluation of changes in concentration in small animals from many collection points. To examine the distribution of a drug to various body components, radiologic methods are also used, which require sequential killing of animals and cannot be applied to human studies. In any case, these methods cannot quantitate the real clearance of special organs (e.g., the difference between pre- and posthepatic circulation) or the dynamic uptake in small but critical compartments of the body (e.g., cerebrospinal fluid).

Ion-selective membrane electrodes have been well researched and are frequently used in the field of analytical chemistry. Some have involved the preparation of a coated-wire type (5–10) because of simplicity of fabrication and manipulation. But analysis in vivo with such a coated-wire electrode has not yet been reported. This is especially true in the case of electrodes that are selective for certain types of clinical drugs. The present report indicates the feasibility of future application of drug-selective electrodes in vivo for pharmacokinetic research.

The coated-wire electrodes that we developed were sensitive to local anesthetics of concentration range 10^{-6} to 10^{-2} mol/L. That the slopes approximate 59 mV/concentration decade at 25°C means that the membranes have good selectivity for the local anesthetic cations and work in accordance with the Nernst equation (Appendix 1).

Although the responsiveness of the electrodes is excellent and slope versus concentration is stable, the relative potential to the reference electrode cannot immediately indicate the absolute concentration. Calibration for each pair of electrodes is always necessary before measurement. Even minute changes in the content of the ion pairs in the membranes during long-term use can affect the general potential shift. The condition of the reference electrode may also change over time. All potentiometric analysis equipment, even pH/mV meters in general use, need calibration before use.

In an alkaline media, the electrode potential decreased as the pH value increased. This is probably due to a decrease in the concentration of the protonated form (or cation) with a corresponding increase of uncharged form (or base) of the local anesthetic. According to the Henderson-Hasselbalch equation for basic drugs, the proportion of cation to total drug (cation + base) is 0.5 when the pH is equal to the pKa of the drug: pH = pKa + log([base]/[cation]). The recently reported pKa values for lidocaine, dibucaine, and mepivacaine at 25°C are 7.91, 8.72, and 7.76, respectively (11). The pH of the solution in which the ratio of cation decreases from 0.5 to 0.05 and 0.005 is calculated from the equation to be pKa + 1.28 and pKa + 2.30, respectively. These decadal changes in cation concentration should show a correspondingly negative shift in the electromotive force with the value of Nernstian slope. This fits well with the alkaline portion of the curves in Figure 4, although the slope of mepivacaine is moderate compared with dibucaine or lidocaine. On the other hand, when the pH decreases by 1 from the pKa, this ratio increases steeply to 91%. When pH decreases by 1.28 or more, the ratio increases to over 95%. Then pH less than 6.5, 7.4, and 6.5 for lidocaine, dibucaine, and mepivacaine, respectively, should make the cation concentration almost constant. This is consistent with our results. Here the concentration of cation equals that of the total drug.

The difference in the hydrophobicity of local anesthetic molecules seems to be responsible for the difference in the electrode potentials among the anesthetics shown in Figure 2. Strichartz et al. (12) reported that the values of the distribution coefficients between *n*-octanol and buffer solution (pH 7.4, 25°C), which reflect the hydrophobicity of the anesthetic molecules, were 1.7, 21, 43, 221, and 346 for procaine, mepivacaine, lidocaine, tetracaine, and bupivacaine, respectively. Fazly Bazaz and Salt (13) reported that the partition coefficients between *n*-octanol and an aqueous medium (pH 6.4, 22°C) were 5.23, 17, and 100 for lidocaine, tetracaine, and dibucaine, respectively, whereas Cassidy et al. (14) reported figures of 9.1 and 33.9 for tetracaine and

Table 3. Potential Characteristics of the Electrodes in Plasmanate

	Anesthetic concentration					
	$10^{-5.5}$ to $10^{-4.5}$ mol/L		$10^{-4.5}$ to $10^{-3.5}$ mol/L		$10^{-3.5}$ to $10^{-2.5}$ mol/L	
Electrode	Potential difference (mV/decade)	CV ($n = 5$) (%)	Potential difference (mV/decade)	CV ($n = 5$) (%)	Potential difference (mV/decade)	CV ($n = 5$) (%)
Lidocaine	11.5	3.0	44.0	1.3	74.5	0.8
Mepivacaine	14.5	2.8	43.5	1.3	72.5	0.8
Dibucaine	5.5	3.2	30.5	1.6	62.0	0.6

CV, coefficient of variation.

dibucaine (pH 7.4, 37°C), respectively. Although these reported partition values vary greatly, presumably owing to the different temperature conditions, ion strengths of the aqueous solutions, or the method of measurement of the local anesthetic concentration, it is true that mepivacaine is more soluble in water than lidocaine, and dibucaine has a much larger partition coefficient for oil than the other local anesthetics. Dibucaine has a butoxyquinoline group instead of a benzene, which accounts for its strong hydrophobicity. The larger the distribution coefficient, the higher the electrode potential or electromotive force, because hydrophobic interaction between the anesthetic cation and the hydrophobic TPB anion becomes stronger. The difference in the selectivity coefficients toward various local anesthetics is also closely related to their lipid solubility as determined by Strichartz et al. (12). The more hydrophobic the electrode's local anesthetic, the less it is interfered with by other local anesthetic molecules. The more hydrophobic the interferent cation, the more it acts on the electrode potential.

As is seen from Figure 5, the potential response in the plasma loses its linearity in the aqueous solution. This is because the local anesthetics bind to albumin and globulin in the plasma, and the free local anesthetic cations decrease. An electromotive force originates only from the free local anesthetic cations and not from the bound ones. In the low-concentration range of local anesthetics, the ratio of the bound to total drug is high, thus depressing the potential response. However, in the high-concentration range, the free fraction increases markedly as the total drug concentration increases; hence the slope of the potential response can be higher than that in protein-free solutions. These effects are remarkable when the affinity of local anesthetics to protein is strong. Dibucaine has a stronger affinity for proteins than lidocaine or mepivacaine, so that its response is more depressed than the others in the low-concentration range. It may be difficult to measure dibucaine concentrations of $<10^{-4}$ mol/L in plasma. However, for lidocaine and mepivacaine, which are drugs in clinical use, the usable range nearly corresponds to the clinical concentration. For example, 10 μg/mL of lidocaine corresponds to $10^{-4.37}$ mol/L. This system is more responsive and useful for the study of the concentration in cerebrospinal fluid, which contains very little protein.

Plasmanate contains the same components as human plasma except for fibrinogen and γ-globulin. The stability and reproducibility without deterioration of the electrode response in Plasmanate are predictable for the practical use of the electrodes in vivo. Of course the influence of fibrinogen and blood cells on the electrodes has to be taken into consideration when we plan their intravascular use, but these electrodes are not likely to accumulate fibrin or coagula easily, because the surface of the electrode tips is quite smooth. They are made by dipping the wire into the membrane gel or epoxy resin and allowing gravity to form a thin, smooth drop shape on the tip when drying. Moreover, measurement in vitro is accompanied by a constant stirring of test solutions in small experimental glass cells; thus, whole blood when used as a test solution can easily provoke hemolysis and requires the addition of anticoagulants. Such experimental conditions are different from normal intravascular bloodstream conditions. The direct application of the electrode in vivo is worth considering as the next experimental step. In our experiment, the coated-wire electrodes were found to be reliable when used repeatedly over several days. In practice, however, we will be able to use and discard a new electrode each time because many electrodes of identical quality made of the same membrane gel can be easily produced at low cost.

The response time of the electrodes of <10 s is reasonable for potentiometric measurement. Still, it may not be fast enough to directly read the fluctuating values in vivo (e.g., plasma drug concentration after intravenous administration). The time taken to be to near equilibrium is shorter than the response time that we determined, as is shown in Figure 3. Hence each potential response can be promptly extrapolated to discern the final value at equilibrium.

The measured potential can be processed with some appropriate calculation to express the final value, which may be practical for analysis in vivo.

There are several advantages with this type of electrode. The absence of inner solutions makes handling and maintenance of the electrodes convenient for daily use. This measuring system is economical because it needs no special equipment or reagent except for a potentiometer with a large internal resistance. The electrodes are very small, and the use of ever-thinner copper wire and flexible fine plastic tubing instead of glass may further miniaturize them in the future and make their insertion into small animals easy. These very small electrodes may find other uses besides pharmacokinetic study. Although most local anesthetic molecules exist in charged form in normal plasma conditions, the uncharged form assumes an important role in the drug effect on organs or cells. The coated-wire ion-selective electrode that responds only to the charged form can be used for the assessment of biological activity in situ of charged and uncharged species separately.

In conclusion, the properties of the coated-wire electrodes are consistent with the electrochemical nature of the local anesthetics. Their small size, stability, and good response in measurement will facilitate their use in vivo.

Appendix 1

Assuming that there is a nonaqueous organic phase (β), with strong hydrophobic anions (A_2^-) (i.e., tetraphenylborate$^-$) and their counter-cations (B^+) (i.e., local anesthetic cation) as ion exchangers, and an adjoining aqueous phase (α) that includes hydrophilic anions (A_1^-) (i.e., Cl^-) and the same cations (B^+), activity of B^+ in the organic phase is fixed by the A_2^-, because A_2^- cannot cross the interface or go into hydrophilic phase because of their hydrophobicity:

$$\begin{array}{c|c} \text{Aqueous phase } \alpha & \text{Organic phase } \beta \\ B^+ \quad A_1^- & B^+ \quad A_2^- \end{array}$$

As long as the concentration of the ion pairs in β is constant, the electric potential difference between these phases depends solely on the activity of B^+ in the aqueous phase and is expressed as follows:

$$\Delta E = 2.303\,(RT/F) \log a_{B(\alpha)} + \text{constant},$$

where $a_{B(\alpha)}$ is activity of B^+ in α, R is the gas constant, F is the Faraday constant, T is temperature (K). This organic phase can be incorporated into a solid membrane of high molecular matrix (i.e., PVC), as mentioned in the text. The Nernstian slope is 59.1 mV/decade in standard situation (25°C), because

$$R = 8.314\ \mathrm{J \cdot mol^{-1} \cdot K^{-1}},$$

$$T = (273 + 25)\ \mathrm{K},$$

$$F = 96.5\ \mathrm{J \cdot mV^{-1} \cdot mol^{-1}}.$$

Appendix 2

If cations of another type (C^+) dissolve in both of the phases, th C^+ cations may act as interferents. The interference relates to th strength of C^+ to purge B^+ from the organic phase and is expresse as

$$B^+(\beta) + C^+(\alpha) \rightleftharpoons B^+(\alpha) + C^+(\beta).$$

The equilibrium constant of this exchange reaction is a function o the Gibbs standard transference energy between α and β of the tw ions. The potential of this ion-selective electrode (E_{ISE}) is ex pressed, finally, in the following Nikolsky equation:

$$E_{ISE} = E_0 + 2.303(RT/Z_DF) \log(a_D + K_{DI}a_I^{Z_D/Z_I}),$$

where a_D is the activity of the drug to be measured; a_I is the activit of the interferent; Z_D is the charge number of the drug; Z_I is th charge number of the interferent; and K_{DI} is the selectivity coefficient of the interferent to the drug.

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Letters to the Editor

The Genioglossus Muscle Belongs Not to Inspiratory But to Expiratory Muscle?

To the Editor:

Respiratory muscles are basically divided into inspiratory and expiratory muscles. Respiratory muscles that discharge in the inspiratory phase belong to the inspiratory group, whereas those in the expiratory phase belong to the expiratory group. The most representative inspiratory muscle is the diaphragm, excitation of which gives a reference of inspiratory phase. Under normal conditions, most of the expiratory muscles are inactive in the expiratory phase. The silent period of the diaphragm usually serves as the expiratory phase.

Ochiai et al. (1) recently reported that among the inspiratory muscles in kittens, the genioglossus, which maintains upper airway patency during inspiration, was most vulnerable to halothane anesthesia. In their article, Figure 1 shows a typical recording of an electromyogram of three inspiratory muscles (diaphragm, intercostal, and genioglossus muscles) during 1% halothane anesthesia in a kitten as a control. If we carefully evaluate each tracing of the figure, we will easily discover that the genioglossus muscle discharged completely out of phase compared with the other inspiratory muscles, the diaphragm and intercostal muscles. This means that this muscle, studied in this experiment, did not belong to the inspiratory muscles. Based on the aforementioned definition, it should belong not to the inspiratory but to the expiratory muscles. In other words, it was not the genioglossus muscle. The genioglossus muscle recorded in adult cats actually discharged in phase with other inspiratory muscle discharges (2).

It must be very difficult to record the activity of a tiny muscle such as the genioglossus in kittens. Probably, expiratory muscle activity was unexpectedly recorded on some occasions. It could be said that some expiratory muscles in kittens are vulnerable to halothane anesthesia.

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Intravenous Halothane—Questions Remain

To the Editor:

Drs. Kawamoto, Suzuki, and Takasaki (1) presented a study of the pulmonary and circulatory effects of intravenous (IV) halothane in dogs. Previous studies have suggested that halothane-induced pulmonary edema is accompanied by structural damage to the pulmonary microvasculature, resulting in increased capillary permeability. In permeability edema, the oncotic pressure gradient is substantially decreased. Therefore, the most important determinant for the development of pulmonary edema is the pressure gradient across the pulmonary microcirculation. Indeed, the authors report increased mean pulmonary artery pressure and pulmonary vascular resistance in the injured lungs, with no significant change in pulmonary arterial occlusion (wedge) pressure or central venous pressure. It has been noted in numerous studies that an elevated capillary pressure can be present despite a normal or subnormal wedge pressure (2–6). The increased lung water measured after IV halothane could have resulted from either hydrostatic or permeability changes or from a combination of both factors. The contribution of the hydrostatic capillary pressure to the development of pulmonary edema and increased extravascular lung water cannot be determined by this study. Moreover, histologic studies were not a part of this study. Therefore, the conclusion reached by the authors that "pulmonary edema induced by IV liquid halothane was due to direct pulmonary vascular damage" is not substantiated.

Second, the authors state that prostaglandin E_1 resulted in myocardial damage. It is unclear how this damage was determined. Although LV dp/dt and SV decreased early in the PGE_1-treated group, which is consistent with depression of myocardial contractility, no evidence was presented to substantiate a claim of myocardial "damage."

Finally, as the authors state in their study, it should be noted that the dose of IV halothane used in this study does indeed represent a massive overdose of halothane compared with customary clinical doses. The injection of 7.5 mmol represents approximately 170 mL of 100% halothane vapor, or about one tidal volume of the dogs studied. The 7% end-tidal concentration indicates that a large volume of halothane was not eliminated during first pass through the lungs. Perhaps an investigation of the cardiopulmonary effects of a smaller IV dose or dilute infusion, with a more

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physiologic end-tidal concentration, might have intriguing implications for the clinical setting.

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Relocation of a Double-Lumen Tube During Patient Positioning

To the Editor:

It is well known that the position of a tracheal tube during anesthesia may be altered by surgical manipulation, patient coughing, or movement of the head, neck, or the entire patient (1–3). We wish to report a case of movement of a double-lumen tube (DLT) from the left to right mainstem bronchus during patient repositioning.

A 61-yr-old man (ASA physical status III) was scheduled for open thoracotomy. Anesthesia was induced with intravenous propofol, and muscle relaxation was achieved with intravenous vecuronium. A 39F left-sided Broncho-Cath (Mallinckrodt) DLT was placed during laryngoscopy. Manual ventilation commenced, and compliance seemed reduced. Auscultation of the axillae revealed right-sided breath sounds when the endobronchial (left) tube was ventilated, and no breath sounds were heard when ventilation via the tracheal lumen was attempted. The DLT was withdrawn to the vocal cords and reintroduced. Ventilation appeared normal, and a "leak test" was performed (4). With the tracheal cuff inflated and the endobronchial cuff deflated, the test indicated successful isolation of each lung. No leak was detected across the endobronchial cuff, and it was therefore left deflated. Controlled mechanical ventilation was commenced, and the DLT was firmly tied in position with a long piece of gauze.

With the anesthesiologist supporting the head, the patient was then turned 90° to the left lateral position and secured by evacuation of air from a large beanbag. Peak airway pressures were then noted to be approximately 40 cm H_2O. Manual ventilation was begun while a flexible fiberoptic bronchoscope was quickly passed through the tracheal lumen. However, on exit from the distal lumen, it came to rest on the tracheal wall. Right mainstem intubation by the endobronchial tube was diagnosed. Meanwhile, the surgeon had made rapid progress and requested deflation of the right lung at this time. Ventilation of the left lung was attempted but was impossible. The bronchoscope was then passed down the endobronchial (left) lumen and the DLT withdrawn slowly. When the carina came into view, the bronchoscope was advanced into the left mainstem bronchus. The DLT was then easily advanced into its correct position. The right lung was then deflated with ease, and surgery proceeded uneventfully.

For the distal end of a DLT to migrate to the contralateral side, several factors need consideration. First, it is likely that the tip of the DLT was not positioned far into the left mainstem bronchus. Flexible bronchoscopy could have been used to optimize tube position before turning. Second, some movements of the head and neck are inevitable during a patient turn, allowing distal tube movement to occur, cephalad and then caudad. Double-lumen tube movement is always possible during turning of patients, and although it has been previoulsy suggested that deflation of the endobronchial cuff should occur to reduce the possibility of mucosal damage (5), relocation of a DLT to the contralateral side has not been recorded. This report, then, describes yet another consequence of movement of a tracheal tube during the turning of patients.

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Removal of a Tenacious Epidural Catheter

To the Editor:

Quite a lot has been written lately about removal of epidural catheters that seem to have become firmly lodged in patients' backs. So, I thought I would offer my words of wisdom on the subject.

I'm sure all of us who perform many epidurals have at some time encountered varying degrees of difficulty in extracting epidural catheters. Of note in the recent literature is a case report by Drs. Sia-Kho and Kudlak in *Anesthesia & Analgesia* (1), advocating extreme flexion of the patient in the lateral decubitus position. This case report reemphasizes Dr. Blackshear's report (2) that more tension is needed to remove epidural catheters with patients sitting versus lying.

Another case report of interest was that of Shantha and Mani (3) in which a sterile Tuohy needle was passed over the epidural catheter and advanced to the epidural space, after which the Tuohy needle and lodged catheter were pulled out together. Although this method was carried out successfully, it has the obvious danger of possibly shearing the catheter and compounding the problem.

I have found on occasion when extreme flexion in the lateral decubitus position was not adequate to facilitate removal of the epidural catheter, that rapidly injecting sterile saline, while at the same time exerting steady traction on the epidural catheter with the patient in the flexed position, enabled removal of the catheter.

It would appear that increasing the turgor of the catheter by continuously filling it with saline, plus lubricating the surroundings of the catheter with the saline, allows the catheter to be released with greater ease.

I hope that this simple technique will be of some clinical value to anesthesiologists who encounter the problem of trapped epidural catheters.

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Cyclosporine A and Cardiopulmonary Bypass

To the Editor:

In a recent case report, Eide and Beflenker (1) described reduced cyclosporine A (CsA) levels with the initiation of cardiopulmonary bypass (CPB). The patient was receiving CsA for 5 yr after renal transplant. We observed similar changes in CsA levels with the initiation of CPB in a patient who underwent CPB surgery 14 mo after liver transplantation and present the data to underscore the role of hemodilution.

The patient, a 56-yr-old, 78-kg man, received CsA (175 mg every 12 h), along with azathioprine (150 mg every day), and prednisone (10 mg every day) for immunosuppression. Plasma CsA levels on the 3 days before surgery were 290, 307, and 275 ng/mL, respectively, on his usual oral dose of CsA. On the morning of surgery, he received oral CsA (175 mg) 6 h before the start of the procedure. Each CsA sample consisted of 4 mL of blood taken from the radial artery catheter and immediately analyzed using a fluorescent immunoassay of a monoclonal antibody to CsA. This technique measures total CsA and does not measure the metabolites. The specificity and sensitivity of this method is >95% and 95%, respectively.

Table 1. Changes in Blood Cyclosporine A Concentration During the Pericardiopulmonary Bypass Time

	Before CPB (min)			During CPB (min)			After CPB (min)	
	135	90	1	14	24	30	3	30
CsA (ng/mL)	553	406	295	259	225	216	240	223
Temp (°C)	35	35	35	28	30	30	35.2	35.6
Hct (%)	39	35	33	18	18	18	18	26

CPB, cardiopulmonary bypass; CsA, cyclosporine A; Temp, temperature; Hct, hematocrit.

In the operating room, CsA samples were drawn before, during, and after bypass. The CsA levels, along with the corresponding temperatures and hematocrits, are shown in Table 1.

In our patient, as in the previous report, CsA levels decreased in the prebypass period. There was a further reduction in the CsA levels with the initiation of CPB. The CsA levels remained decreased during the postbypass period (Table 1).

Although there are many factors that may alter the pharmacokinetics of a drug, factors uniquely associated with CPB are dilution of red blood cells and plasma proteins via the pump priming volume, hypothermia, and binding to the bypass circuit on membrane oxygenator. Most evidence suggests that the latter two do not appear to be important (2,3).

The most likely explanation for the decreases in CsA noted is hemodilution because this would explain the reduced CsA levels before, during, and after bypass. The major contribution to the dilution of course is the pump prime, which in our case consisted of 2500 mL of plasmalyte A, 100 mL of 25% albumin, and heparin (7300 U), although the 1100 mL of crystalloid administered before CPB accounted in part for the decrease before bypass along with continued metabolism.

Nevertheless, because chronic administration of CsA results in accumulation of tissue stores in the peripheral compartment (3), it is unlikely that the decreased levels seen intraoperatively in patients on such chronic CsA therapy are clinically significant, and the intraoperative monitoring of CsA levels may not be useful.

More important, although these decreases are noted in two patients who underwent CPB, this decrease in CsA levels and hemodilution can occur in many other patients not undergoing CPB if a large amount of volume of either blood or cystalloid is administered. Such patients receiving short-term therapy may experience an acute lowering of CsA levels, which may affect organ survival.

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Touchscreen Technology: Potential Source of Cross-Infections

To the Editor:

Documented cross-infection by contaminated anesthesia equipment is relatively rare. There is no agreement on how much sterilization should be attempted between cases, but most would agree that meticulous cleaning of the nondisposable components of the anesthesia machinery is imperative after use in patients suspected of harboring an infectious organism (1).

The introduction of touchscreen technology, demanding more hands-on contact with the anesthesia machine and equipment (2,3), may have increased the possibility for cross-infections in the operating room. These potentially contaminated surfaces represent an expansion of the interaction among the patient, the anesthesiologist, and the machinery. If neglected and not properly cleaned, they can potentially become the source of infections.

These surfaces of some modern anesthesia equipment may be regarded as just a monitor and not as a frequently touched control surface. Consequently, these superficies may not be properly disinfected after each case to prevent cross-contamination. It is recommended that one refer to the manufacturer's cleaning instructions for disinfection, because these surfaces may be damaged by certain chemicals. Given the fact that immunosuppressed patients are increasingly undergoing surgical procedures (4), it is prudent to assume that only the best disinfection and sterilization standards will control the spread of disease.

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Unexpected Results: Consider a Medication Error

To the Editor:

McLean et al. (1) report the failure of negative aspiration, a test dose with epinephrine, a test done with 100 μg of fentanyl, and fractionation of the local anesthetic dose in detecting migration into a vein by an epidural catheter that had been working well for 4 h previously.

Their evidence for intravascular injection is a seizure after 18 mL of 2% lidocaine with 1:200,000 epinephrine administered over 12 min. The seizure developed 2 min after the last dose of local anesthetic was administered via the catheter.

If this was indeed a case of catheter migration, it would be highly unusual. Four usually successful methods of detecting intravascular injection would have failed in the same patient, including the administration of 90 μg of epinephrine intravenously without a significant change in heart rate and 100 μg of fentanyl that had no effect on sensorium. In addition, the 2-min delay in the onset of a seizure after the last fractionated dose and the very modest dose of lidocaine administered allow one to consider other plausible causes for this clinical picture.

I believe that the course of events depicted may best be explained by a medication error. Physician-prepared lidocaine (pH adjusted) and multiple test doses with different agents give ample opportunity for error. Succinylcholine was present in the operating room and was used when this patient was urgently converted to a general anesthetic. Medication errors with epidural catheters do occur. There is a long list of medications that have erroneously been injected into the epidural space (2–4). The events in this case presentation are consistent with an epidural injection of succinylcholine. I have heard the exact words that this patient uttered before "seizing" in a patient given 10 mg of succinylcholine when awake ("What's happening to me?").

Although this patient's adverse result could have been related to an overdose of intravenous lidocaine, I believe that a medication error must also be considered and would recommend that this be part of any differential diagnosis where a drug does not perform as expected.

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In Response:

Thank you for the opportunity to respond to Dr. Groudine's letter. I disagree with his conclusion that the case report (1) may be best explained by a medication error.

Dr. Groudine believes that the events in our case presentation are consistent with an epidural injection of succinylcholine, in part because he heard an awake patient given 10 mg of succinylcholine say the exact words that our patient used before "seizing." Dr. Groudine did not mention by what route the succinylcholine was administered to his patient. Although I have no personal experience in the administration of 10 mg of succinylcholine to awake patients by any route, I am quite sure that the phrase, "What's happening to me," is not pathognomonic of its use.

In addition after the administration of the last 5-mL dose of pH-adjusted 2.0% lidocaine with 1:200,000 epinephrine, the patient described in our report had an unmistakable grand mal seizure. This was not succinylcholine-induced fasciculations. In fact, her muscle tone was markedly increased, and it was necessary to paralyze her with succinylcholine (100 mg) to be able to intubate the trachea and to ventilate her.

I agree with Dr. Groudine that medication errors with epidural catheters do occur and that a medication error should be considered whenever a drug does not perform as expected. I do not believe that a medication error occurred in the case that we described. Rather, the case report (1) demonstrates that it may not always be possible to detect an intravascular placement or migration of an epidural catheter.

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Laryngeal Mask Airway in Cervical Spine Injuries

To the Editor:

We read with interest the correspondence by Day (1) and Hastings (2) with regard to the use of the laryngeal mask airway (LMA) in patients with cervical spine injury and wish to take issue with some of the points raised.

The LMA has been successfully used in airway management in *elective* cases with cervical spine injury and disease (3) but is contraindicated when aspiration of gastric contents is possible because it may not, in all cases, protect the airway from contamination. However, in situations where immobilization of the cervical spine is required, conventional tracheal intubation may be impossible, and the LMA may prove a safer alternative than mask ventilation (where the airway is completely unprotected). The small risk of aspiration when using the LMA is outweighed by the disastrous consequences of hypoxemia secondary to failed tracheal intubation. We believe the LMA should always be available for managing the difficult airway and should be used before transtracheal ventilation or cricothyroidotomy (4).

Although we would agree with Hastings (2) that the LMA is inappropriate as a first-line airway management device in *emergencies* and in cases with laryngeal injury or edema, we cannot endorse his opinion that the LMA has a high complication rate. "Epiglottic obstruction" has not been reported with the LMA. Epiglottic *downfolding* is commonly observed when a fiberoptic bronchoscope is passed through the LMA (5), but ventilation is not impaired. Laryngospasm and coughing are avoidable if an adequate anesthetic depth has been obtained, and most studies report a 90%–95% success rate after one insertion attempt using the LMA, even when the operators are unskilled (6).

We have recently submitted for publication in this journal a study comparing both the ease of intubation and the time taken to successfully ventilate with the LMA and tracheal tube in patients immobilized in a rigid cervical collar. Our findings (as yet unpublished) suggest that the LMA is an easier and faster method of securing the airway. The relatively atraumatic insertion of the LMA imparts less force to the cervical spine than a difficult laryngoscopy. Extrapolation to the field scenario where patients may be combative, obese, or have full stomachs can only be speculative, but nevertheless, we believe that the LMA should be available if rapid, gentle tracheal intubation using a laryngoscope and in-line stabilization of the neck is impossible. We concur with Hastings (2) that further studies, particularly of outcome, are warranted.

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4. Benumof JL. Management of the difficult adult airway. Anesthesiology 1991;75:1087–1110.
5. Nandi PR, Nunn JF, Charlesworth CH, Taylor SJ. Radiological study of the laryngeal mask. Eur J Anaesthesiol 1991;4(Suppl):33–9.
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In Response:

My letter was directed against use of the LMA as a first-line airway management technique in emergencies. I believe that the contraindications are the risk of aspiration and the possibility of inadequate airway control. If the LMA does not work properly, the anesthesiologist must manipulate the patient's airway, head, and neck a second time, under what may be more trying circumstances. Studies have been published in which LMA use was associated with airway obstruction (1,2), possibly secondary to epiglottic downfolding (1). Difficulty with ventilation, especially if high airway pressures are required, is another potential problem. I agree that the LMA may be an alternative in the event of a failed tracheal intubation. The safety of any airway management technique for patients with injured cervical spines is speculative without studies of the amount of spine movement during execution and the resultant clinical outcome. I thank Drs. Pennant, Gajraj, and Pace for their comments, and I await publication of their study.

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2. Maltby JR, Loken RC, Watson NC. The laryngeal mask airway: clinical appraisal in 250 patients. Can J Anaesth 1990;37:509–13.

Is Your Scavenger System Functional?

To the Editor:

The scavenging of anesthetic waste gas according to OSHA standards is a vital part of protecting the operating room personnel from the adverse effects of breathing residual anesthetic agents. We would like to report the finding in our institution of numerous machines with inoperable scavenging systems on random survey.

Recently, we purchased 10 Narkomed 2B anesthesia systems equipped with an open scavenging system. Our previous machines used the traditional closed scavenging systems that were familiar to our anesthesia providers. The closed system utilized a spring-loaded valve for positive and negative pressure relief. The open system, however, uses continually open ports to provide positive and negative pressure relief. The open system, when connected to suction and in the functional position, makes an audible sound that may have caused operating room personnel to disconnect or inactivate the system to eliminate the sound.

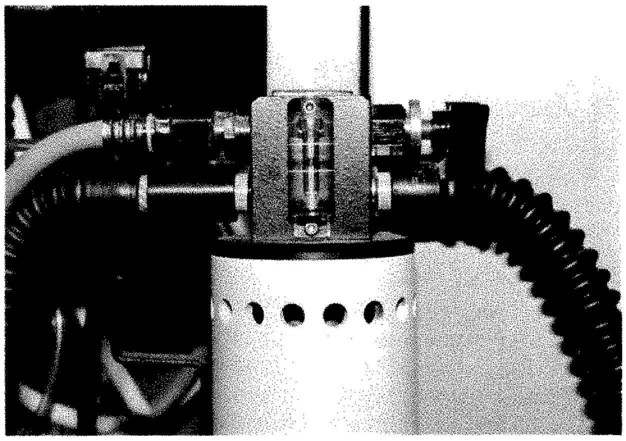

Figure 1. Narkomed 2B showing correct position for functioning scavenger system.

On a random survey, we found that 10 of 10 anesthesia systems were being used with the scavenging device in the "off" mode. The head technician at Narkomed Inc. reported that if the machine is used with the scavenger system in the off position, the anesthetic gases accumulate in the chamber and spill into the room, polluting the operating room environment.

Figure 1 indicates the correct "on" position with the "ball" in between the two white lines. We would like to emphasize that the scavenging system is a routine part of the anesthetic machine checkout. However, we have consistently noted that the system is turned off by operating room personnel.

We hope that our reporting this to the anesthesia community will prevent exposing operating room personnel to anesthetic agents and thereby assist them to conform to OSHA standards.

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Epidural Kits: Incompatible Contents

To the Editor:

I recently reported a problem associated with the use of a particular epidural needle (1). On two occasions, the plastic hubs on these needles cracked during use. We stated that these needles were manufactured by Burron Medical. This is incorrect. When we were testing a number of different needles for use in our department, the faulty needles were kept for later inspection. Later, as a result of a breakdown in communication between our purchasing department and myself, Burron Inc. was named as the manufacturer. The needles in question were in fact manufactured by Portex.

We are now using Burron epidural needles and have experienced no problems with them. The hub on the Burron needle is resistant to cracking because it is made of Polycarbonate.

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Reference

1. Patterson KW. Epidural kits: incompatible contents (letter). Anesth Analg 1992;74:474.

Section Editor
Norig Ellison

Book Reviews

Clinical Anaesthetic Pharmacology

John W. Dundee, R. S. J. Clarke, and William McCaughey, eds. New York: Churchill Livingstone, 1991, 627 pp, $89.00, ISBN 0-4430-2073-6.

The practice of anesthesia begins and ends with pharmacology; it is not possible to separate one from the other. Therefore, textbooks of applied pharmacology should be the foundation on which anesthetic expertise is based. Surprisingly, there have been only a few attempts to produce a comprehensive text on anesthetic pharmacology, and there is no true market leader as there has been for other subjects within the practice of anesthesia.

The present offering was conceived as an authoritative text on the pharmacology of anesthetic drugs, with a strong scientific foundation but relating also to everyday practice. It has been written largely by the staff of the University Department of Anaesthesia, Belfast, with 28 total contributors. The fact that so many are well known is a credit to the productivity of this department under the guidance of the senior editor while he was head of the department.

The 36 chapters that make up the text are grouped in six sections: Basic, Central Nervous System, Peripheral Nervous System, Cardiovascular System, Other Systems, and Special Drug Problems in Patient Management. The chapters themselves vary in size from 8 to 30 pages of text, and each is referenced with approximately one page of references per chapter. The most recent reference in the pharmacokinetics chapter is 1988, and 1990 in the anesthetic gases chapter.

Each chapter attempts to highlight the basic data of pharmacology, such as the pharmacokinetics and pharmacodynamics, as well as include details of clinical use. This attempt at a comprehensive review has a superficial appeal, but it has the inherent weakness that advances in knowledge in different disciplines occur at different rates. Therefore some aspects of the text will need to be revised more often than others. For example, only one paragraph is devoted to sevoflurane and 18 lines to desflurane, whereas more than one page each is devoted to chloroform, diethyl ether, and trichloroethylene. Ondansetron receives fewer lines of text than acupuncture in the management of emesis. Cisapride and terfenadine are not indexed at all. Propanidid and alphaxolone are described, but pregnanolone is not.

Throughout the text, the interests of the senior editor are emphasized, and there is much information about intravenous agents, premedicants, benzodiazepines, the influence of age on drug disposition, and acupuncture. The formulas of most, if not all, drugs are given, and there are illustrations to guide the reader in mechanisms of action, rate of onset, and duration of action of drugs.

The subject matter of this book is accurate and well presented as far as it goes. More modern aspects of anesthetic pharmacology are omitted or covered only superficially (e.g., pharmacokinetic/pharmacodynamic modeling, design of intravenous dosage regimens, novel drug delivery). This is a pity, not only because it diminishes the value of the book in modern anesthetic practice, but also because it does not reflect the life and work of Professor Dundee who was at the forefront of anesthetic pharmacology research for so many years. This reviewer regrets that this book, produced after Professor Dundee's retirement, should appear to be quite old-fashioned and out of date almost from its date of publication.

British textbooks do not usually sell very well in the United States for a variety of reasons (e.g., drug names may be different, dosages and anesthetic regimens may vary, and the examination structure is different from the United Kingdom). There has been no obvious attempt to make this book appropriate for the U.S. anesthesiologist. Although some will find this book useful, it is not comprehensive, and other sources of reference will be required by most anesthetists.

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A Manual for Acute Postoperative Pain Management

F. B. Sevarino and L. M. Preble. New York: Raven Press, 1992, 242 pp, $55.00.

Although pain in the postoperative period is commonly encountered, that symptom complex has received little attention until recently. Today, in part because of quality of life issues, both patients and medical staff consider postoperative pain management an important issue. As an example of this, at the 1992 Annual Meeting of the Japanese Society of Anesthesiologists, a symposium on postoperative pain attracted many anesthesiologists and generated considerable interest.

This reviewer believes that postoperative pain management should be started preoperatively. For example, premedication and personal contact with the patient are very important determinants of postoperative pain. Intraoperatively balanced anesthesia with analgesics and general anesthesia supplemented with epidural anesthesia may also contribute to postoperative pain relief. This manual does not address either preoperative or intraoperative management of postoperative pain relief. However, a vari-

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ety of methods for postoperative pain management are described, such as intravenous patient-controlled analgesia and spinal opioids.

The authors' aim is to outline the establishment of an acute pain service, which will provide a team of clinical specialists to manage acute pain. The manual consists of two parts. The first part outlines the basics of planning analgesic therapy in Chapters 1–5. The second part discusses patient management in Chapters 6–12. Each part has appendices that address nursing education, policies and procedures, guidelines, credentialling, physician and patient education, and various record/flow sheets (in the first part) and drugs and their indications in acute pain management as well as products and company addresses (in the second part). These appendices will be very useful for those who are setting up an acute pain service.

A student or inexperienced resident will find the manual educational because of the many illustrations and detailed explanations. The manual is highly recommended to all who are interested in acute pain, especially those who are in the process of setting up an acute pain service.

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Clinical Procedures in Anesthesia and Intensive Care

J. L. Benumof, ed. Philadelphia: J.B. Lippincott, 1992, 972 pp, $125.00, ISBN 0-3975-0950-2.

Atlas of Procedures in Anesthesia and Critical Care

J. F. Butterworth IV. Philadelphia: W.B. Saunders, 1992, 256 pp, $30.00, ISBN 0-7216-2916-4.

Although the titles of these two books may appear similar, their purposes differ. It is hardly fair to compare them, for each book merits individual attention.

Clinical Procedures in Anesthesia and Intensive Care is wonderful! It is such a beautiful book, you may want to display it on your coffee table. This comprehensive text contains practically everything you need to know about almost all modern clinical procedures. Benumof has recruited 45 contributors; many are anesthesiologists, others are cardiologists, surgeons, neurosurgeons, urologists, obstetricians, gynecologists, pediatricians, nurses, and bioengineers.

Butterworth's *Atlas of Procedures in Anesthesia and Critical Care* is exactly that—an atlas. Clear and concise, it is intentionally limited to the essentials.

Benumof states in the Preface to *Clinical Procedures in Anesthesia and Intensive Care* that his goal is "to bring together in one book a description of all modern clinical procedures that anesthesiologists must be familiar with." The book does precisely that. Its 44 chapters are grouped into six sections according to the basic system treated: Preparing and Using the Anesthesia Machine, Respiratory Procedures, Cardiovascular Procedures, Central Nervous System Procedures, Peripheral Nerve Procedures, and Gastrointestinal, Obstetric, and Renal Procedures. *Clinical Procedures in Anesthesia and Intensive Care* contains wonderful illustrations, photographs, tables, graphs, x-rays, and even a few xerograms. There are 27 color plates taken from interesting transesophageal echocardiograms, as well as a color figure obtained from a Lifescan EEG analyzer during cross-clamping of the carotid artery. Chapters are uniformly organized with Introduction, Indications, How to do the procedure (along with reasonable alternatives), Discussion, Complications, and References. Chapters are centered around "how to do it," with each step carefully detailed for the reader. This book is a pleasure to read and own.

Although many topics might seem to overlap, the text is rarely redundant. We were hard put to find any problems, but the chapter on pulmonary artery catheterization makes no distinction between relative indications and absolute indications. Perhaps this is best illustrated by the statement, "Patients with progressive renal insufficiency despite conservative therapy should have PA catheterization unless the cause of renal deterioration is known to be untreatable." Progressive renal insufficiency, as they have defined it, is not a widely accepted *absolute* indication for PA catheterization. Overall, the chapters are very well written and contain many pearls that cannot be found in another single source. For example, the chapter on transtracheal ventilation describes the technique with clear photographs (that have illustrations superimposed), as well as a detailed discussion of equipment that can be used in an emergency situation.

Butterworth's *Atlas of Procedures in Anesthesia and Critical Care* contains 31 chapters divided into four sections: Airway Management, Intravascular Cannulation, Regional Anesthesia, and Positioning the Patient on the Operating Room Table. This book was not planned to be all-inclusive but to "illustrate the more representative regional anesthetic, airway management, invasive monitoring, and positioning techniques in one volume." The illustrations were done by one artist; this makes it clean and easy to follow. The text accompanying the illustrations is intentionally limited to essentials. Each procedure is handled individually and organized as such. This atlas does not pay as much attention to detail as does Benumof's text, but the essentials are clearly discussed. The book is well indexed to facilitate its use as a quick reference. There is a most interesting chapter on positioning patients. This atlas is very easy to read. It makes an excellent teaching guide for medical students and residents.

In short, both Drs. Benumof and Butterworth have succeeded in attaining the different goals that they each set out to accomplish. Both books will find a place in departmental libraries. Butterworth's *Atlas of Procedures in Anesthesia and Critical Care* will serve well as a quick reference for operating rooms and intensive care units. In contrast, Benumof's *Clinical Procedures in Anesthesia and Intensive Care* is a complete reference guide that every anesthesiologist and intensivist will want to own personally. Despite its cost, it is a great investment. Watch your copy—your friends may "liberate" it.

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Prehospital Emergency Medicine

J. Schou. Lorrach, Germany: Alix, 1992, 348 pp, $60.00, ISBN 3-928811-01-0(D).

Although it may seem strange to review a book on prehospital emergency care in an anesthesiology journal, *Prehospital Emergency Medicine* is written by an anesthesiologist who discusses a subject quite appropriate for anesthesiologists. The author points out that when he was assigned to work on an emergency helicopter service in 1981 as part of his duties as an anesthetist in Northern Germany, he essentially had to learn from his own experience. This book is based on his experience in prehospital emergency medicine (PHEM) and is designed and written to act as a guide to clinical practice rather than as a theoretical textbook of PHEM. As an anesthesiologist reading this book, this reviewer was impressed that the skills required to practice PHEM successfully are similar to the skills required to practice anesthesia successfully. This book will help anesthesiologists to broaden their professional horizons and to realize that our discipline's activities are not confined to the operating room for perioperative care of the surgical patient but also involve prehospital care of emergency patients.

The author uses his personal experience instead of extensive laboratory research to provide material for this book. It is quite apparent when reading the book that the author has "been there" and has learned much from extensive personal experience with PHEM. The book is organized in section format with short, easy to read subsections or chapters. The organizational themes of the chapters in the seven sections are arranged to cover the scope of practice of PHEM as well as to develop some of the qualifications for physicians practicing this speciality.

The book depends heavily on case reports to illustrate important points. These case reports include both positive and negative outcomes and are particularly well chosen to illustrate needed teaching points. The author has used not only case reports from his own experience but also those from other providers. Besides developing the scope of practice of PHEM, the case illustrations also address the advantages of providing a physician on the scene for emergency care.

Section A develops the theme of three principal tasks of PHEM—diagnosis, therapy, and assignment (patient disposition). These tasks are developed throughout the rest of the book. Choice of a suitable receiving clinic and vehicle for transport is included in assignment. This section also discusses the difficult issue of triage and treatment priorities during mass casualties and disasters. Sections B through E cover therapy during PHEM in great detail, beginning with resuscitative skills. Following the discussion of resuscitation in Section B, the author covers therapy for diseases, beginning with life-threatening injuries in Section C, and emergency therapy of diseases in Section D. Section E covers miscellaneous emergencies, including obstetric emergencies, drowning, electrical accidents, and environmental emergencies.

Section F covers organization and formalities and Section G supplies and security. The term security is used to mean not only security of patient care but security for personnel providing the patient care in a hostile environment. Included in this section are safety tips for helicopter and rescue missions. There are several appendices that cover a personal tribute to Henning Ruben (the developer of the self-inflating resuscitation bag), abbreviations used in the book, a drug index, conversion factors, and a general index.

Some of the important issues covered in the book that are unique in the anesthesia literature are rescue techniques, including extrication of the injured from difficult scenes. Special problems of managing patients in the helicopter as well as safety tips on how to avoid injury to medical personnel by the helicopter are also covered. The special problems of land transport by ambulance, a useful list of supplies needed for emergency medical practice, and the pros and cons of different drugs for use in the prehospital area are also covered in the book. The book also covers organizational issues, and Chapter F,5 discusses the thorny issue of when is the physician required in the prehospital arena. The duties of a physician in the field are thoroughly covered, with a differentiation between triage from disasters versus the assignment of single casualties to an appropriate medical facility. Again, this section is well illustrated with clinical examples demonstrating both potential good outcomes and poor outcomes.

The quality of the book is reasonable, with a sewn binding and hard cover that appears to be sturdy. The pages are generally printed well and easy to read; however, I was disappointed that my copy came with a few blank pages, which may suggest some quality assurance problems with the publishing company.

Who would benefit from the purchase of this book? As an anesthesiologist with a strong interest in trauma care, this reviewer found the book fascinating to read and would recommend it to anyone who is interested in knowing more about the care of the injured patient. The concept of providing the ultimate preoperative anesthetic consult for the trauma patient by going to the scene of the accident is exciting. The International Trauma Anesthesia and Critical Care Society (ITACCS), founded following the 9th World Congress of Societies of Anesthesiology in Washington, D.C. in 1988, has members who are involved in just such endeavors in different countries around the world. These anesthesiologists are witness to the wisdom of anesthesiologists taking their practice to the field to treat injured and acutely sick patients.

This book should also be on the shelves of libraries in anesthesia departments that maintain a residency program. Many of the problems discussed in providing prehospital emergency care are the same problems encountered by anesthesia residents responding to "Code" calls in various locations inside and outside the hospitals they work in. A reading of pertinent sections in this book would help the residents solve the problems that they encounter in this risky task of extending anesthesia care outside of the operating room.

In summary, this is a well-written, important book that covers a facet of anesthesia practice that is common in Europe but very uncommon in the United States. It is also one of the few books to describe in detail clinical lessons from prehospital practice. Furthermore, there are many good clinical lessons in this book that can be applied to our current anesthesia practice in the United States, which is increasingly expanding out from the operating room.

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Epidural and Spinal Anaesthesia With Bupivacaine: Effects of Age on Neural Blockade and Pharmacokinetics

B. T. Veering. Leiden: University Hospital Leiden, 1991, 217 pp.

This is not really a textbook. This doctoral thesis provides an excellent summary of the current state of knowledge about the influence of aging on bupivacaine regional blockade. As such, it is a reference rather than a text and may not be practical for the clinician but would be a useful addition to the library of the academic anesthesiologist, particularly one who deals with regional anesthesia.

The core of the book is a presentation of the author's eight research projects on the issue of the effects of aging on bupivacaine pharmacokinetics and pharmacodynamics during epidural and spinal anesthesia and the implications for toxicity. These articles summarize the current state of knowledge in this area and contain an excellent review of the other data collected on this subject. The gathering of all of the research findings in one manuscript (previously published in six separate journals) is very helpful. Although this book is ostensibly limited to a discussion of bupivacaine, the format adds an excellent review of the problems of aging on anesthetic pharmacokinetics and pharmacodynamics. This first chapter is applicable to many other drugs and situations other than bupivacaine behavior. Chapters 5–12 repeat the specific publications, as mentioned. This leads to a certain redundancy in the references and discussions but allows each chapter to "stand alone" in addressing its specific question.

The presentation is clear and pleasant reading. Only rarely is the English idiom stretched, such as the description of the quality of neural blockade as "feeble." Overall, this book contains a wealth of information and can serve as the current definitive reference on the questions of age and bupivacaine epidural and spinal anesthesia.

There are shortcomings. The format of repeating the scientific papers makes for an erratic flow of thought. The conclusion section serves as an excellent summary but is almost too brief. The absence of an index makes it difficult to find the answer to very specific questions without reading entire pages and sections. The book is also frustrating in its limited scope. Although bupivacaine is covered well, there are only intermittent references to the previous data on lidocaine pharmacokinetics and pharmacodynamics. Naturally, there will be questions soon about ropivacaine also. More important, these studies do not address the issues of the pharmacokinetics and pharmacodynamics of epidural or spinal opioids in the elderly, which has become a common question in current practice. These questions were clearly beyond the scope of this dissertation, but their absence is tantalizing.

In summary, this is an excellent review of the current knowledge on this specific subject. It is a useful reference for the academician (especially the regional anesthesiologist) but may not be practical for the clinician.

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Perioperative Myocardial Ischemia and Infarction, Volume 30, No. 1 of the International Anesthesiology Clinics

Charles Beattie and Lee A. Fleisher, eds. Boston: Little, Brown, 1992, 258 pp, $81.00 (annual subscription).

Perioperative Myocardial Ischemia and Infarction is a well written, up to date, clinically oriented monograph dealing with the detection, pathophysiology, and current treatment of myocardial ischemia and infarction in the perioperative period. In this issue of International Anesthesiology Clinics, well-known contributing authors have written 14 separate articles devoted to four primary management issues: (1) the detection of myocardial ischemia and risk assessment using continuous electrocardiography, echocardiography, and dipyridamole-thallium scintigraphy; (2) mechanisms and potential causes of perioperative myocardial ischemia; (3) prophylaxis and treatment of myocardial ischemia; and (4) pathogenesis, diagnosis, and treatment of perioperative myocardial infarction. In this regard, the overall approach of the editors, Beattie and Fleisher, is fairly traditional and customary; so much so, that this monograph bears a striking resemblance to two earlier efforts that appeared in a competing clinics format (Clinics of North America in 1988 and 1991). Reasonable questions then arise—How does this particular monograph fit in with similar works that preceded it—and along with this—Does this work represent new and unique material, or is it merely a leg-weary rehash of old information?

The Beattie and Fleisher monograph duplicates to a small degree the work of J. G. Reeves, which appeared in Clinics of North America in September 1988. This repetition is noticeable in the articles devoted to the detection of ischemia using electrocardiography, the role of hemodynamics and anesthetic technique in perioperative myocardial ischemia, and the cardiologist's treatment of acute myocardial infarction. The marked similarity in the articles devoted to echocardiography and to the treatment of ischemia and myocardial protection is not surprising because each article is authored by the same person in both monographs.

In contrast, the Beattie and Fleisher monograph is quite different from the work of Peter Duke, which appeared again in Clinics of North America in September 1991. In the latter, the emphasis heavily favors the fundamentals of basic coronary anatomy and physiology as well as the cellular and biochemical effects of myocardial ischemia in relation to ventricular function. Duke's monograph also includes excellent articles devoted to silent ischemia, risk assessment, and management of right and left ventricular dysfunction.

What emerges as the main strength and most cogent reason for purchasing the Beattie and Fleisher monograph are the articles dealing with perioperative risk assessment and perioperative factors contributing to myocardial ischemia and infarction. First, the stage is set with an overview of the existing literature with regard to the relationship between perioperative myocardial ischemia and infarction. This is followed by an excellent article concerning the use of ambulatory electrocardiography for the detection of myocardial ischemia as well as its use as a screening tool before noncardiac surgery. The article on dipyridamole-thallium scintigraphy is especially outstanding and runs the gamut from describing thallium uptake and its response to dipyridamole to its use as a preoperative screening test to assess cardiac risk. This article very nicely summarizes the existing literature to date.

Last, but not least, the articles dealing with the various perioperative factors that may contribute to myocardial ischemia are truly the crown jewels of the monograph. These include individual articles on the stress response, oxygen-carrying capacity, circadian variation in coronary vasomotion, and perioperative hemostatic changes that cause a hypercoagulable state. The unifying theme here is decreased myocardial oxygen supply secondary to factors that promote coronary thrombosis and vasospasm as well as atherosclerotic plaque rupture. These articles are an intriguing tour de force that focuses attention on the emerging importance of the postoperative period in the pathogenesis of myocardial ischemia and infarction.

In summary, *Perioperative Myocardial Ischemia and Infarction* is a well-done, very clinically relevant work. It merits thoughtful consideration by any clinician or intensivist serious about improving the perioperative care of patients with known or suspected ischemic heart disease.

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Books Received

Receipt of the books listed below is acknowledged. Selected books from this list will be reviewed in future issues of the Journal.

The Journal solicits reviews of new books from its readers. If you wish to submit a review, before proceeding please send a letter of intent, identifying the book in question, to Dr. Norig Ellison, Department of Anesthesia, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104. The Journal reserves the right of final decision on publication.

Atlee JL, Gombotz H, Tscheliessnigg KH, eds. *Perioperative Management of Pacemaker Patients*. New York: Springer Verlag, 1992, 155 pp, $59.00, ISBN 0-387-53874-7.

Bissonnette B, ed. *Cerebral Protection, Resuscitation, and Monitoring. A Look into the Future of Neuroanesthesia*. Volume 10, No. 3 of Anesthesia Clinics of North America, Philadelphia: W.B. Saunders, 1992, 300 pp, $78.00 annual subscription, ISSN 0889-8537.

Cane RD, Davison R, Albrink MH, eds. *Handbook of Critical Care Procedures and Therapy*. St. Louis: Mosby Year Book, 1992, 393 pp, $37.95, ISBN 0-8016-6555-8.

Davey A, Moyle JTB, Ward CS. *Ward's Anaesthetic Equipment*, 3rd ed. Philadelphia: W.B. Saunders, 1992, 391 pp, $35.00, ISBN 0-7020-1435-4.

Galford RE. *Problems in Anesthesiology, Approach to Diagnosis*. Boston: Little Brown and Company, 1992, 451 pp, $45.00, ISBN 0-316-30289-9.

Herbert DW. *Drugs in Anesthesia and Critical Care*. Philadelphia: W.B. Saunders, 1992, 346 pp, $24.95, ISBN 0-7216-4583-6.

Liu PL, ed. *Principles and Practice in Anesthesiology*. Philadelphia: J.B. Lippincott, 1992, 448 pp, $65.00, ISBN 0-397-50948-0.

Miller RD, Abram SF, Kirby RR, Ostheimer GW, Roizen MF, Stoelting RK. *Year Book of Anesthesia and Pain Management 1992*. St. Louis: Mosby Year Book, 1992, 466 pp, $59.95, ISBN 0-8151-5938-2.

Monroe GL. *A Handbook for the Traveling Freelance Physician*. Houston: Magellan Publishing Company, 1992, 156 pp, $75.00.

Nichols DG, Yaster M, Lappe DG, Buck JR, eds. *Golden Hour, The Handbook of Advanced Pediatric Life Support*. St. Louis: Mosby Year Book, 1992, 447 pp, $29.95, ISBN 0-8151-6395-2.

Omoigui S. *The Anesthesia Drug Handbook*. St. Louis: Mosby Year Book, 1992, 352 pp, $29.95, ISBN 0-8016-6898-0.

Pullerits J, Holzman RS, eds. *Anesthesia Equipment for Infants and Children*. Volume 30, No. 3 of International Anesthesiology Clinics, Boston: Little Brown and Company, 1992, 195 pp, $81.00 annual subscription, $39.00 single issue, ISBN 0-316-42389-0.

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Danae Powers, M.D.
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David Rothenberg, M.D.
Ass't. Prof. of Anesthesiology
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Assoc. Prof. of Anesthesiology
University of Florida

Written Board Review

Lectures and written exam seminars

- February 2-7 and April 12-17
- Home-study keywords with discussions and questions with answers.
- Six-day lecture with syllabus.
- Seminars for written exam questions.

Oral Board Review

Mock oral exams and lectures

- February 2-7 and April 12-17
- Home-study, oral-exam stem cases with pre-op, intra-op and post-op questions.
- Six-day lectures with syllabus and concurrent mock oral exams most hours.
- **Registration includes one mock oral.**
- Extra public mock oral exam ($80), private mock oral exam ($110).

Oral Board Tutorial Days

Choose any days – groups limited to 24

- February 12-15 and every weekend January 9-April 20: call for schedule
- Home-study, oral-exam stem cases with pre-op, intra-op and post-op questions.
- Mock oral exams in groups **limited to 24.**
- **Includes one public mock oral per day.**
- Extra public mock oral exams ($80), private mock oral exams ($110).

Two-Part Board Review

Nine mock orals in any two courses

- Any course in 1993, plus any other within three years. One course may be up to six Oral Board Tutorial days of your choice.
- Choose between lectures and concurrent mock orals or written exam discussions.
- **Nine mock oral exams in groups limited to 24 participants.**

Unconditional Guarantee

- If you fail the next Anesthesiology Board Exam you take after taking one of these courses, we will refund half of your last course registration fee and allow you to repeat the course once for FREE.

Limited Enrollment: ANESTHESIOLOGY REVIEW COURSE REGISTRATION

Name ______________________________
Address ______________________________
City/State ______________________________
Zip ________ Phone ____________________

☐ Feb. 2-7, '93 – Tampa
☐ Feb. 12-15, '93 – Los Angeles
☐ April 12-17, '93 – Seattle
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(800) 356-7537
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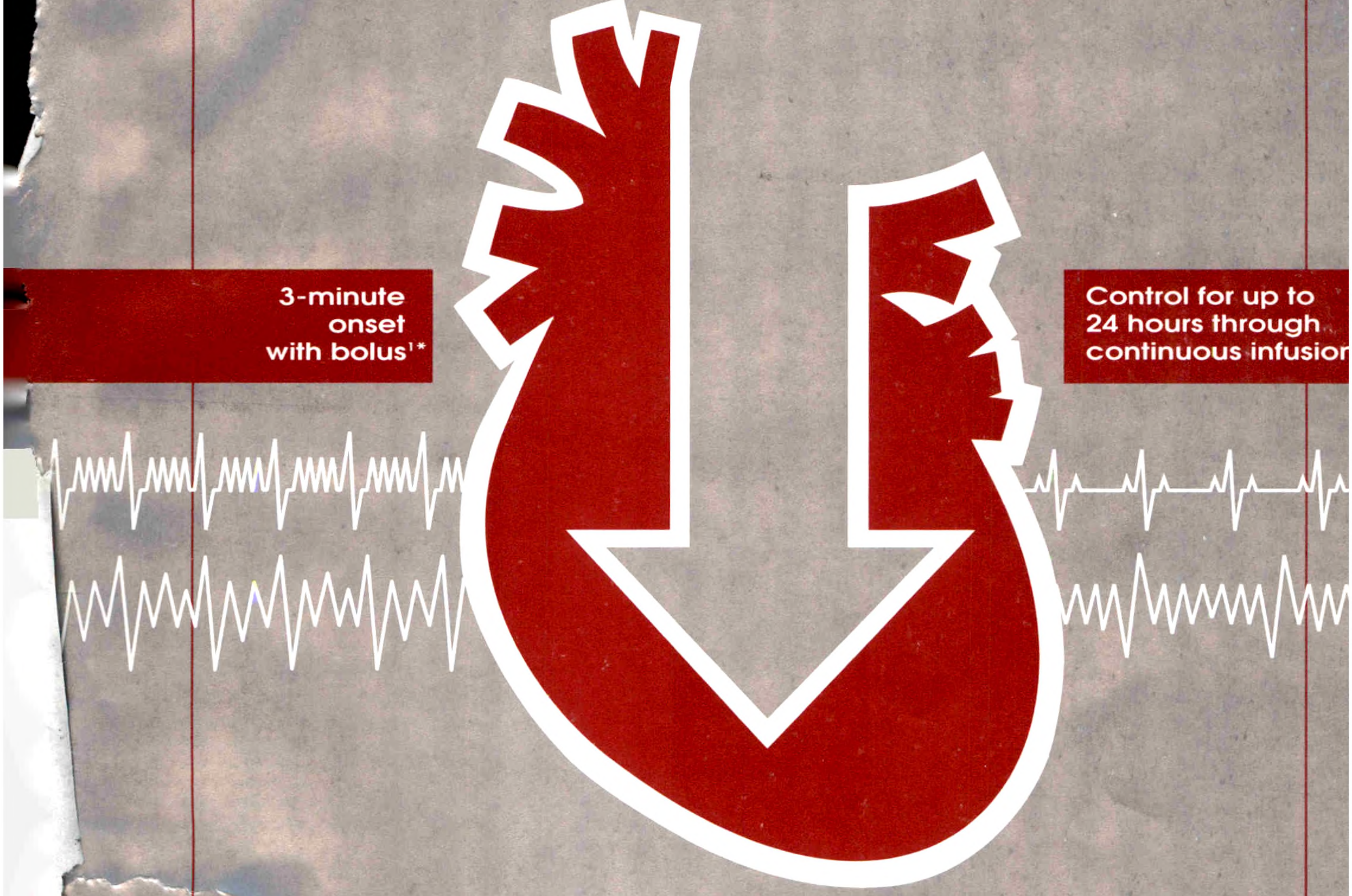
Now for heart rate control during atrial fibrillation and flutter

CARDIZEM® *Injectable*
(diltiazem hydrochloride)
BOLUS INFUSION
5 mg/mL



3-minute onset with bolus[1]*

Control for up to 24 hours through continuous infusion

Heart rate control that is
FAST, SAFE, AND CONTINUOUS[1,2†]

Cardizem Injectable is indicated for temporary control of rapid ventricular rate during atrial fibrillation and flutter; rarely converts to normal sinus rhythm; should be used with continuous monitoring of ECG and blood pressure to avoid hypotension or bradycardia. Infusion rate/dose should be regulated accordingly. A defibrillator and emergency equipment should be readily available.

*Symptomatic hypotension (3.2%) or flushing (1.7%) occurs most often during or immediately following bolus injection.
†Contraindications: atrial fibrillation and flutter patients with WPW or short PR syndrome; sick sinus syndrome or second- or third-degree AV block, except with a functioning pacemaker; severe hypotension or shock; hypersensitivity; recent IV beta-blockers; ventricular tachycardia.

Please see the brief summary of prescribing information on an adjacent page.

CIVAH497/A8114

6491E2

CARDIZEM® Injectable
(diltiazem hydrochloride)
BOLUS INFUSION

CONVENIENT DOSAGE

1 Beginning treatment as

BOLUS: 0.25 mg/kg actual body weight **over 2 minutes**

20 mg average patient

2 If response is inadequate, wait 15 minutes

BOLUS: 0.35 mg/kg actual body weight **over 2 minutes**

25 mg average patient

3 Treatment as

INFUSION:
10* to 15 mg/hr

*5 mg/hr may be appropriate starting infusion for some patients.

BRIEF SUMMARY

CARDIZEM® Injectable

(diltiazem hydrochloride)

INDICATIONS AND USAGE

CARDIZEM Injectable (diltiazem hydrochloride) is indicated for the following:

1. ***Atrial Fibrillation or Atrial Flutter.*** Temporary control of rapid ventricular rate in atrial fibrillation or atrial flutter. It should not be used in patients with atrial fibrillation or atrial flutter associated with an accessory bypass tract such as in Wolff-Parkinson-White (WPW) syndrome or short PR syndrome.
2. ***Paroxysmal Supraventricular Tachycardia.*** Rapid conversion of paroxysmal supraventricular tachycardias (PSVT) to sinus rhythm. This includes AV nodal reentrant tachycardias and reciprocating tachycardias associated with an extranodal accessory pathway such as the WPW syndrome or short PR syndrome. Unless otherwise contraindicated, appropriate vagal maneuvers should be attempted prior to administration of CARDIZEM Injectable.

The use of CARDIZEM Injectable for control of ventricular response in patients with atrial fibrillation or atrial flutter or conversion to sinus rhythm in patients with PSVT should be undertaken with caution when the patient is compromised hemodynamically or is taking other drugs that decrease any or all of the following: peripheral resistance, myocardial filling, myocardial contractility, or electrical impulse propagation in the myocardium.

For either indication and particularly when employing continuous intravenous infusion, the setting should include continuous monitoring of the ECG and frequent measurement of blood pressure. A defibrillator and emergency equipment should be readily available.

In domestic controlled trials in patients with atrial fibrillation or atrial flutter, bolus administration of CARDIZEM Injectable was effective in reducing heart rate by at least 20% in 95% of patients. CARDIZEM Injectable rarely converts atrial fibrillation or atrial flutter to normal sinus rhythm. Following administration of one or two intravenous bolus doses of CARDIZEM Injectable, response usually occurs within 3 minutes and maximal heart rate reduction generally occurs in 2 to 7 minutes. Heart rate reduction may last from 1 to 3 hours. If hypotension occurs, it is generally short-lived, but may last from 1 to 3 hours.

A 24-hour continuous infusion of CARDIZEM Injectable in the treatment of atrial fibrillation or atrial flutter maintained at least a 20% heart rate reduction during the infusion in 83% of patients. Upon discontinuation of infusion, heart rate reduction may last from 0.5 hours to more than 10 hours (median duration 7 hours). Hypotension, if it occurs, may be similarly persistent.

In the controlled clinical trials, 3.2% of patients required some form of intervention (typically, use of intravenous fluids or the Trendelenburg position) for blood pressure support following CARDIZEM Injectable.

In domestic controlled trials, bolus administration of CARDIZEM Injectable was effective in converting PSVT to normal sinus rhythm in 88% of patients within 3 minutes of the first or second bolus dose.

Symptoms associated with the arrhythmia were improved in conjunction with decreased heart rate or conversion to normal sinus rhythm following administration of CARDIZEM Injectable.

CONTRAINDICATIONS

CARDIZEM Injectable is contraindicated in:

1. Patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker.
2. Patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker.
3. Patients with severe hypotension or cardiogenic shock.
4. Patients who have demonstrated hypersensitivity to the drug.
5. Intravenous diltiazem and intravenous beta-blockers should not be administered together or in close proximity (within a few hours).
6. Patients with atrial fibrillation or atrial flutter associated with an accessory bypass tract such as in WPW syndrome or short PR syndrome.

   As with other agents which slow AV nodal conduction and do not prolong the refractoriness of the accessory pathway (eg, verapamil, digoxin), in rare instances patients in atrial fibrillation or atrial flutter associated with an accessory bypass tract may experience a potentially life-threatening increase in heart rate accompanied by hypotension when treated with CARDIZEM Injectable. As such, the initial use of CARDIZEM Injectable should be, if possible, in a setting where monitoring and resuscitation capabilities, including DC cardioversion/defibrillation, are present (see OVERDOSAGE). Once familiarity of the patient's response is established, use in an office setting may be acceptable.
7. Patients with ventricular tachycardia. Administration of other calcium channel blockers to patients with wide complex tachycardia (QRS ≥ 0.12 seconds) has resulted in hemodynamic deterioration and ventricular fibrillation. It is important that an accurate pretreatment diagnosis distinguish wide complex QRS tachycardia of supraventricular origin from that of ventricular origin prior to administration of CARDIZEM Injectable.

WARNINGS

1. **Cardiac Conduction.** Diltiazem prolongs AV nodal conduction and refractoriness that may rarely result in second- or third-degree AV block in sinus rhythm. Concomitant use of diltiazem with agents known to affect cardiac conduction may result in additive effects (see Drug Interactions). If high-degree AV block occurs in sinus rhythm, intravenous diltiazem should be discontinued and appropriate supportive measures instituted (see OVERDOSAGE).
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function and in patients with a compromised myocardium, such as severe CHF, acute MI, and hypertrophic cardiomyopathy, have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Administration of oral diltiazem in patients with acute myocardial infarction and pulmonary congestion documented by x-ray on admission is contraindicated. Experience with the use of CARDIZEM Injectable in patients with impaired ventricular function is limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM Injectable therapy may occasionally result in symptomatic hypotension (3.2%). The use of intravenous diltiazem for control of ventricular response in patients with supraventricular arrhythmias should be undertaken with caution when the patient is compromised hemodynamically. In addition, caution should be used in patients taking other drugs that decrease peripheral resistance, intravascular volume, myocardial contractility or conduction.
4. **Acute Hepatic Injury.** In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted following oral diltiazem. Therefore, the potential for acute hepatic injury exists following administration of intravenous diltiazem.
5. **Ventricular Premature Beats (VPBs).** VPBs may be present on conversion of PSVT to sinus rhythm with CARDIZEM Injectable. These VPBs are transient, are typically considered to be benign, and appear to have no clinical significance. Similar ventricular complexes have been noted during cardioversion, other pharmacologic therapy, and during spontaneous conversion of PSVT to sinus rhythm.

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. The drug should be used with caution in patients with impaired renal or hepatic function (see WARNINGS). High intravenous dosages (4.5 mg/kg tid) administered to dogs resulted in significant bradycardia and alterations in AV conduction. In subacute and chronic dog and rat studies designed to produce toxicity, high oral doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver, which were reversible when the drug v discontinued. In dogs, oral doses of 20 mg/kg were also associated w hepatic changes; however, these changes were reversible with continu dosing.

Dermatologic events progressing to erythema multiforme and/or exfoliative dermatitis have been infrequently reported following oral diltiazem. Therefore the potential for these dermatologic reactions exists following exposure t intravenous diltiazem. Should a dermatologic reaction persist, the drug should be discontinued.

Drug Interactions. Due to potential for additive effects, caution is warranted in patients receiving CARDIZEM Injectable concomitantly with any agent(s) known to affect cardiac contractility and/or SA or AV node conduction (see WARNINGS).

As with all drugs, care should be exercised when treating patients with multiple medications. CARDIZEM undergoes extensive metabolism by the cytochrome P-450 mixed function oxidase system. Although specific pharmacokinetic drug-drug interaction studies have not been conducted with single intravenous injection or constant rate intravenous infusion, coadministration of CARDIZEM Injectable with other agents which primarily undergo the same route of biotransformation may result in competitive inhibition of metabolism.

Digitalis: Intravenous diltiazem has been administered to patients receiving either intravenous or oral digitalis therapy. The combination of the two drugs was well tolerated without serious adverse effects. However, since both drugs affect AV nodal conduction, patients should be monitored for excessive slowing of the heart rate and/or AV block.

Beta-blockers: Intravenous diltiazem has been administered to patients on chronic oral beta-blocker therapy. The combination of the two drugs was generally well tolerated without serious adverse effects. If intravenous diltiazem is administered to patients receiving chronic oral beta-blocker therapy, the possibility for bradycardia, AV block, and/or depression of contractility should be considered (see CONTRAINDICATIONS). ***Oral*** administration of diltiazem with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. In vitro, propranolol appears to be displaced from its binding sites by diltiazem.

Anesthetics: The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium blockers should be titrated carefully.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats at oral dosage levels of up to 100 mg/kg/day, and a 21-month study in mice at oral dosage levels of up to 30 mg/kg/day showed no evidence of carcinogenicity. There was also no mutagenic response in vitro or in vivo in mammalian cell assays or in vitro in bacteria. No evidence of impaired fertility was observed in a study performed in male and female rats at oral dosages o up to 100 mg/kg/day.

Pregnancy. Category C. Reproduction studies have been conducted in mic rats, and rabbits. Administration of oral doses ranging from five to ten time greater (on a mg/kg basis) than the daily recommended oral antiangina therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In th perinatal/postnatal studies there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human oral antianginal dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. Diltiazem is excreted in human milk. One report with oral diltiazem suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

The following adverse reaction rates are based on the use of CARDIZEM Injectable in over 400 domestic clinical trial patients with atrial fibrillation/flutter or PSVT under double-blind or open-label conditions. Worldwide experience in over 1,300 patients was similar.

Adverse events reported in controlled and uncontrolled clinical trials were generally mild and transient. Hypotension was the most commonly reported adverse event during clinical trials. Asymptomatic hypotension occurred in 4.3% of patients. Symptomatic hypotension occurred in 3.2% of patients. When treatment for hypotension was required, it generally consisted of administration of saline or placing the patient in the Trendelenburg position. Other events reported in at least 1% of the diltiazem-treated patients were injection site reactions (eg, itching, burning)—3.9%, vasodilation (flushing)—1.7%, and arrhythmia (junctional rhythm or isorhythmic dissociation)—1.0%.

In addition, the following events were reported infrequently (less than 1%):

Cardiovascular:	Atrial flutter, AV block first degree, AV block second degree, bradycardia, chest pain, congestive heart failure, sinus pause, sinus node dysfunction, syncope, ventricular arrhythmia, ventricular fibrillation, ventricular tachycardia.
Dermatologic:	Pruritus, sweating.
Gastrointestinal:	Constipation, elevated SGOT or alkaline phosphatase, nausea, vomiting.
Nervous System:	Dizziness, paresthesia.
Other:	Amblyopia, asthenia, dry mouth, dyspnea, edema headache, hyperuricemia.

Although not observed in clinical trials with CARDIZEM Injectable, other reactions associated with oral diltiazem may occur.

Product information as of October 1991

MARION MERRELL DOW INC.
PRESCRIPTION PRODUCTS DIVISION
KANSAS CITY, MO 64114

References: 1. Cardizem Injectable prescribing information.
2. Ellenbogen KA, Dias VC, Plumb VJ, Heywood JT, Mirvis DM. *J Am Coll Cardiol.* 1991;18:891-897.

CARDIZEM INJECTABLE...HEART RATE CONTROL THAT IS FAST, SAFE, AND CONTINUOUS

Classified Advertising

OHIO
Anesthesiologist, University Hospitals. Must be at least board eligible. Equal Opportunity, Affirmative Action Employer. Send curriculum vitae to Helmut F. Cascorbi, MD, PhD, Professor and Chairman, Department of Anesthesiology, University Hospitals of Cleveland, 2074 Abington Road, Cleveland, OH 44106.

701E/L

ILLINOIS: ANESTHESIOLOGIST
To join congenial group of MDs/CRNAs expanding to provide anesthesia coverage for only hospital in city since recent merger. No open heart or neurosurgery. Environment conducive to family living, variety of schools, recreation. Good opportunity with stable future. City located in east central Illinois with population of approximately 40,000 (35-mile radius service area with 126,126 population). Within driving distance of Chicago and Indianapolis. Please send CV to Box 887D/L.

887D/L

CARDIOVASCULAR FELLOWSHIP OPPORTUNITY
The Department of Anesthesiology and Critical Care Medicine at the University of New Mexico School of Medicine has openings at the CA-4 level for advanced training in cardiovascular anesthesiology. The fellowship is a 2-year comprehensive program designed to train the fellow for a career in cardiovascular anesthesiology. Research in cardiovascular physiology and anesthesia, provision of clinical care for complex adult and pediatric cases, participation in conference, and teaching responsibilities are part of the fellowship experience. Interested individuals should send CV or contact Jorge A. Estrin, MD, PhD, Professor and Chairman, Department of Anesthesiology, University of New Mexico School of Medicine, Albuquerque, NM 83131-5216, (505) 272-2610, FAX (505) 277-1300. The University of New Mexico is an Equal Opportunity/Affirmative Action Employer.

912F/L

THE UNIVERSITY OF NEW MEXICO
Department of Anesthesiology and Critical Care Medicine has immediate faculty positions at the Instructor, Assistant Professor, Associate Professor, and Professor levels for candidates with experience in cardiac, obstetric, neurosurgical, and pediatric anesthesia and critical care medicine. Responsibilities include the teaching of medical students and residents and the provision of clinical care in a busy tertiary referral center. Opportunities to pursue research interests will be provided. It is expected that candidates who apply for CCM positions will have or be eligible for subspecialty certification. Qualified candidates should send CV or contact Jorge A. Estrin, MD, PhD, Professor and Chairman, Department of Anesthesiology, University of New Mexico School of Medicine, Albuquerque, NM 87131-5216, (505) 272-2610, FAX (505) 277-1300. The University of New Mexico is an Equal Opportunity/Affirmative Action Employer.

913F/L

CALIFORNIA
University of California, Irvine: Openings for faculty positions in the Department of Anesthesiology. (1) Assistant or associate professor level in the in-residence series. Responsibilities include teaching and research. (2) Clinical instructor and assistant professor level in the clinical series. Responsibilities include teaching and clinical service. Participation in research is highly desirable but not mandatory

Rank and pay commensurate with skills and experience. Faculty will serve at both a tertiary-care university hospital and a VA Medical Center. Candidates must be ABA certified, or in the examination process, and be eligible for a California state license. An Affirmative Action, Equal Opportunity Employer. Address correspondence with references and curriculum vitae to Steven J. Barker, PhD, MD, Chair, Department of Anesthesiology, University of California, Irvine Medical Center, 101 City Drive South, Route 81A, Orange, CA 92668.

930G/L

LOUISIANA STATE UNIVERSITY MEDICAL CENTER—SHREVEPORT
Faculty positions available for board certified/eligible anesthesiologists. Duties include patient care, resident and student teaching, supervision of CRNAs, research, and administrative responsibilities. Faculty rank and salary commensurate with experience. Please send curriculum vitae and names of three references to D. Richard Davis, II, MD, Associate Professor and Chairman, Department of Anesthesiology, LSU Medical Center—Shreveport, 1501 Kings Highway, Shreveport, LA 71130-3932. We are an Equal Opportunity/Affirmative Action Employer.

931G/L

ANESTHESIOLOGIST
Multispecialty group of 43 physicians adjacent to 165-bed hospital in need of BC/BE anesthesiologist. Located in West Texas City of 80,000 with excellent recreational activities. Salary guarantee with bonus based on production. Send CV to West Texas Medical Associates, 3555 Knickerbocker Road, San Angelo, TX 76904.

936H/A

NEW ORLEANS
Louisiana State University Medical Center, Department of Anesthesiology, is seeking a board-certified anesthesiologist who is interested in directing publications and research. Outstanding opportunities for clinical studies are available. No night call, weekends, or holidays are required. Excel-

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CLASSIFIED ADS

Anesthesia & Analgesia makes available classified advertising space for those interested in obtaining positions or wishing to announce meetings, postgraduate courses, or other pertinent events. We require that all advertisements be relevant to the practice of anesthesia and analgesia, and we reserve the right to refuse advertisements that are not relevant.

Specifications. Ads should be typewritten on letterhead stationery; the text should be double-spaced, with the title or key phrase typed in capital letters. Enclose two photocopies with each ad. Display space (minimum ¼ page) is available through Pharmaceutical Media, Inc., 440 Park Avenue South, 14th floor, New York, NY 10016, telephone: (212) 685-5010, FAX: (212) 685-6126.

Rates. Ads cost $1.50 per word per insertion, with a minimum of 20 words. Abbreviations, dates, initials, post office box numbers, telephone numbers, years, and zip codes are considered one word each. There is an additional fee of $18.00 per insertion for box number ads.*

Payment. Full payment or institutional purchase order must accompany the copy for each ad. Ads received without a check or purchase order will be returned. (Make checks payable to Elsevier Science Publishing Companv, Inc.)

Deadline. Copy must be received 7 weeks before publication date (i.e., by January 1 for the March issue); multiple-insertion ads are welcome. Ads may run up to 6 months per purchase order/payment. Please specify in which issue(s) your advertisement is to appear.

Send all ad copy, payments, and correspondence to: *Anesthesia & Analgesia*, Classified Ads, Desk Editorial, Elsevier Science Publishing Co., Inc., 655 Avenue of the Americas, New York, NY 10010.

*When responding to a box number ad, include the box number on all correspondence.

lent salary and fringe benefits. Eligibility for Louisiana licensure is prerequisite. Please send curriculum vitae to M. Naraghi, MD, Professor and Chairman, LSU Department of Anesthesiology, 1532 Tulane Avenue, New Orleans, LA 70140. LSUMC is an EEO/AA employer.

937H/A

POSTDOCTORAL FELLOWSHIP
Background in clinical medicine or clinical research required for studies with patients with heart disease undergoing surgery. Cardiac function and ischemia assessed with ECG, Holter, and echocardiography monitoring. Working with cardiologists, epidemiologists, and anesthesiologists. Send CV and names of three references to Dennis T. Mangano, PhD, MD, Professor and Vice Chairman, Department of Anesthesia, University of California, San Francisco, 4150 Clement Street (129), San Francisco, CA 94121.

949H/L

BC/BE anesthesiologist for a 500-bed tertiary hospital in a Florida coastal city. Immediate opening. Liberal salary and early partnership. Send resume to Box 956I/L.

956I/L

COASTAL NEW JERSEY—ANESTHESIOLOGIST DESIRED
Immediate opening for BC or BE MD/DO to join an expanding group practice of 10 MDAs and 9 CRNAs covering a 500-bed regional medical center composed of two hospitals performing over 9000 anesthetics. All types of anesthesia except OH. Great opportunity for energetic well-trained individual. Unlimited opportunity and outstanding lifestyle in a family-oriented seashore community. Very competitive financial package. Please reply with CV to S. Hernberg, DO, Chairman, Department of Anesthesiology, 1925 Pacific Avenue, Atlantic City, NJ 08401.

958I/L

UCSF PEDIATRIC ANESTHESIOLOGY FELLOWSHIP
The Departments of Anesthesia at the University of California, San Francisco and Children's Hospital of Northern California, akland, California are jointly offering two -year clinical fellowship positions (CA-4) pediatric anesthesiology beginning *July* 993. The fellowship will include extensive perating room experience in all pediatric bspecialties in both institutions and critl care medicine exposure for both neotes, older infants, and children. The fels will spend 6 months in each titution. Send inquiries to Dolores olz, Postdoctoral Coordinator, Department of Anesthesia, University of California, San Francisco, Box 0648, San Francisco, CA 94143-0648.

967I/L

ILLINOIS
Thirty-two physician, well-established, single-specialty group of anesthesiologists seeks additional anesthesiologists. Challenging, broad-based practice encompasses all surgical subspecialties at three hospitals and three ambulatory facilities. Excellent benefits with early partnership. Please send CV to Associated Anesthesiologists, S.C., 5401 North Knoxville, Suite #49, Peoria, IL 61614.

979J/C

MID-SOUTH: ANESTHESIOLOGIST
Immediate opening for BC/BE anesthesiologist at a modern 600-bed teaching hospital and major referral center located in the mid-south. Practice includes cardiac, thoracic, vascular, and general anesthesia as well as intensive care. No obstetrics or pediatrics. Group is to consist of six (6) doctors and 18 CRNAs. Please reply to Clifton W. Emerson, MD, Cardiovascular Anesthesiologists, P.C., 4230 Harding Road, Suite 509, Nashville, TN 37205. Please enclose your current CV.

980J/L

FELLOWSHIP—CARDIAC ANESTHESIOLOGY
CA-3 or CA-4 fellowship position now available in cardiac anesthesia. Busy open heart and vascular service. Opportunity for OR, cath lab, ICU, and clinical research. Excellent salary/benefit package. Send inquiries with CV to Anthony A. Ascioti, MD, Department of Anesthesiology, St. Joseph's Hospital Health Center, 301 Prospect Avenue, Syracuse, NY 13203.

984J/A

ANESTHESIOLOGIST
Opening for BC/BE anesthesiologist to join MD/CRNA group in small midwestern university town. Area abounds in lakes, forests, wildlife, and recreational activities. Within easy driving distance to large metropolitan area. Working environment very stable and congenial. All surgical specialties represented except hearts and neuro. Salary commensurate with experience. Please reply with CV to Box 990K/D.

990K/D

MICHIGAN
BE/BC anesthesiologist to join busy 3 MD/7 CRNA group in southeastern Michigan lakeside community of 75,000. Excellent schools and family environment within 35 minutes of three large metropolitan areas. No open heart, minimal neuro. Salary and attractive benefit package first 24 based on experience, leading to partnership offer. Send curriculum vitae and two references to Box 992K/B.

992 K/B

NEW YORK
CA-3 and CA-4 positions at Memorial Sloan-Kettering Cancer Center beginning July 1993. Advanced clinical and clinician-investigator opportunities available in critical care medicine, pain management, and anesthesia for thoracic surgery. Send CV and summary of career goals to Roger S. Wilson, MD, Chairman, Department of Anesthesiology and Critical Care Medicine, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021.

994KL

BC Anesthesiologist, 44, experienced in all techniques including OB, regional, and invasive monitoring seeks quality group or individual practice. Good references. Call (216) 372-5959.

995K/A

ANESTHESIOLOGISTS
Temple University School of Medicine has full-time faculty positions available for board-eligible anesthesiologists with training in a subspecialty area (Cardiac Anesthesia, Critical Care and/or Pain). Faculty rank will be commensurate with experience. Duties include patient care, teaching, and research. Send curriculum vitae to Christer Carlsson, MD, PhD, Chairman, Department of Anesthesiology, Temple University School of Medicine, Broad & Ontario Streets, Philadelphia, PA 19140. An Equal Opportunity, Affirmative Action Employer.

996KL

CONTINUING EDUCATION SOCIETY
1993 Scientific Foundations of Anesthesia Board Reviews. Written courses: Jan 2–9; Mar 6–13; May 1–8; June 19–26. Oral courses: Feb 27–Mar 6, Apr 3–10. For more information call (800) 344-2093.

997K/J

ANESTHESIOLOGIST BE/BC to provide physician anesthesia at an academic medical center. Flexible schedule, no call. TJU is an Affirmative Action/Equal Opportunity Employer. Interested parties should contact: Joseph L. Seltzer, MD, Professor and Chairman, Department of Anesthesiology, Thomas Jefferson University, Philadelphia, PA 19107.

1000K/A

FELLOWSHIP—OBSTETRIC ANESTHESIA
Fellowship

clinical care included. Please send letter with CV and references (3) to Harvey Carp, PhD, MD, Department of Anesthesiology, Oregon Health Sciences University, 3181 S.W. Sam Jackson Park Road, Portland, Oregon 97201. Telephone: (503) 494-5223; Fax: (503) 494-4588.

1001K/A

FELLOWSHIP—PEDIATRIC ANESTHESIOLOGY
The Department of Anesthesiology for the Medical College of Wisconsin is accepting applications for 12-month subspecialty training in pediatric anesthesiology beginning July 1, 1993 (CA-3 and CA-4 positions are available). Experience and training will include all aspects of pediatric anesthesiology including cardiac anesthesia and pain management. Opportunity also is provided for clinical research and critical care experience. Inquiries, CV, and references should be sent to Stephen P. Pontus, MD, Section of Pediatric Anesthesiology, Children's Hospital of Wisconsin, PO Box 1997, MS 735, Milwaukee, Wisconsin 53201. Equal Opportunity/Affirmative Action Employer M/F/D.

1008KL

EAST CENTRAL INDIANA
Anesthesiologist needed to join group of nine MDs serving two large hospitals. No open heart or neuro. Fee for service; low malpractice. Located 45 miles from downtown Indianapolis. Contact (317) 378-6654 or reply to PO Box 4237, Anderson, IN 46013.

1010KL

UNIVERSITY OF ARIZONA, DEPARTMENT OF ANESTHESIOLOGY, PHOENIX CAMPUS AT MARICOPA MEDICAL CENTER
Is growing and seeking qualified, board certified/board eligible anesthesiologists for the following positions: Pediatric Anesthesia, Critical Care, Cardiac Anesthesia, and Directors of Pain Management and of Respiratory Therapy. Responsibilities include patient care, teaching, research, and administration. Please forward curriculum vitae and three references to Jerry M. Calkins, PhD, MD, Clinical Professor and Chairman, Department of Anesthesiology, Maricopa Medical Center, 2601 East Roosevelt, PO Box 5099, Phoenix, AZ 85010. Equal Opportunity Employer.

1011K/D

NORTHCENTRAL PENNSYLVANIA
BC/BE Anesthesiologist to direct an Anesthesia Department of three CRNAs at a progressive rural community hospital. Located in the beautiful mountains of Potter County, well known for outdoor recreational activities, this community is an ideal setting for the family. Competitive salary guarantee. Excellent practice opportunity. Please send CV to Jan Freeman Knisley, Physician Recruiter, Charles Cole Memorial Hospital, RR1, Box 205, Coudersport, PA 16915-9762; or call (814) 274-9300, ext 486, or (814) 274-0229.

1012K/A

WANTED: TWO ANESTHESIOLOGISTS at the Instructor or above level. Must have an MD degree, completed a 4-year residency in anesthesiology, have documentation in research fellowship or postgraduate training, and be board certified or board eligible. The positions have an anticipated starting date of February 1, 1993 or later. Stipend negotiable and dependent on credentials. Interested parties should forward letter including board status, curriculum vitae, and bibliography to Salvatore R. Goodwin, MD, Search Committee Chairman, Department of Anesthesiology, University of Florida College of Medicine, PO Box 100254, Gainesville, FL 32610-0254. Application deadline for position is January 15, 1993. Equal Employment Opportunity/Affirmative Action Employer.

1013KL

WANTED: CLINICAL ANESTHESIOLOGIST at the Clinical Instructor, Clinical Assistant Professor or Clinical Associate Professor level. Must have an MD degree, completed a 4-year residency in anesthesiology, have documentation in research fellowship or postgraduate training, and be board certified or board eligible. The position has an anticipated starting date of February 1, 1993 or later. Stipend negotiable and dependent on credentials. Interested parties should forward letter including board status, curriculum vitae, and bibliography to Salvatore R. Goodwin, MD, Search Committee Chairman, Department of Anesthesiology, University of Florida College of Medicine, PO Box 100254, Gainesville, FL 32610-0254. Application deadline for position is January 15, 1993. Equal Employment Opportunity/Affirmative Action Employer.

1014KL

PEDIATRIC ANESTHESIOLOGIST
The Nemours Children's Clinic, a pediatric tertiary-care subspecialty clinic, located on the St. Johns River in Jacksonville, Florida, is seeking a staff pediatric anesthesiologist. Nemours is a partner in a consortium, including the new Children's Hospital, for the development of a Regional Pediatric Medical Center. In order to provide innovative services and additional patient care in a new Children's Hospital, Nemours is expanding its Department of Anesthesiology. Candidates must be BC/BE in anesthesiology, with a pediatric anesthesiology fellowship or the equivalent in experience. Proximity to First Coast beaches, cultural and recreational opportunities, and year-round mild climate, as well as an opportunity for professional growth and participation in research and resident educatio make this a very desirable employme choice. The recruiting deadline is 2/1/9 Interested applicants should send CV Dr. Richard Helffrich, Jr., Chairma Search Committee, Nemours Children Clinic, 807 Nira Street, Jacksonville, F 32207, (904) 390-3766. Nemours is an Equ Opportunity Employer.

1015K

PAIN MANAGEMENT CAREER OPPORTUNITY—FLORIDA/TEXAS
New career opportunity in pain manag ment for anesthesiologist. For more info mation call Richard Tinsley, Multidiscipl nary Pain Systems, Inc., 1/800/365-0619.

1016K/

PAIN MANAGEMENT SPECIALIST seeking BE/BC anesthesiologist with pain fellow ship. Join young progressive anesthesiolo gist in postop, chronic and acute pain man agement. Emphasis on lifestyle. Option t work four to twelve months per year. Fou season climate in rural setting. Send CV t Box 1017 K/A.

1017K/

ANESTHESIOLOGIST 8 yr experience in a general and regional anesthesia. Comfor able with all types of anesthesia. Fellow ship in OB. All offers considered, willing t relocate. Licensed in NJ, NY, Florida, Illi nois, Pennsylvania, Michigan, Iowa. Repl to Box 1018 K/B.

1018K/

UNIVERSITY OF ARIZONA
Expanding University program creates ex citing opportunities for new faculty, both academic (tenure) and clinical tracks. Ap plicants must be interested in academi career. Interested particularly in cardiac obstetric, ICU, and pediatric subspecialties An AA/EOE. Contact: Burnell R. Brown Jr., MD, PhD, Department of Anesthesiol ogy, Arizona Health Sciences Center, Tuc son, AZ 85724. Closing date: 6/30/93 o until position is filled.

1020K/C

ANESTHESIOLOGIST/PAIN MANAGEMENT (PORTLAND, OREGON)
Northwest Permanente, P.C., a stable multispecialty group providing care fo 380,000 members of Kaiser Permanente, i seeking a BC/BE anesthesiologist to join group of 9 anesthesiologists and 27 CRNA at our 220-bed Sunnyside Medical Center one of two Kaiser medical centers in the Portland area. Group provides full range o anesthesia services except for open heart.

Special interest: Pain Management, fel lowship trained. Join two other trained MDs part-time in a growing Chronic Pain

Clinic with dedicated time, clinical procedure-room space, and an OR block for fluoroscopy procedures. The department has ongoing research projects in both pain and anesthesia and is preparing a book manuscript on pain.

Stimulating professional environment, beautiful recreation area with easy access to mountains and beaches. Excellent salary and benefits including paid malpractice, sabbatical, two pension plans, and more. Please forward CV to Fred M. Nomura, MD, Regional Medical Center, NORTHWEST PERMANENTE, P.C., 2701 N.W. Vaughn, Suite 300, Portland, OR 97210-5398. EOE.

969IKL

Seeking MDA for group practice. Competitive salary. Early partnership. Crime-free community. Good schools. Close to major airport, colleges, universities. Year-round sports hunting, fishing. Central New York. Reply to: PO Box 459, Oneonta, NY 13820.

1022L

INDIANA

A position is available for a pediatric anesthesiologist at the assistant or associate professor level, clinical or tenure tract, in the Department of Anesthesia, Indiana University School of Medicine. Candidates must have experience in pediatric anesthesia and be in the examination system or board certified. Individual appointed to the tenure track will be required to maintain an active and ongoing research program. Please send curriculum vitae to Robert K. Stoelting, Professor and Chairman, Department of Anesthesia. Indiana University School of Medicine, 1120 South Drive, Fesler Hall 204, Indianapolis, IN 46202-5115. Indiana University is an Equal Opportunity Employer.

1023L

ANESTHESIOLOGIST

Marshfield Clinic Department of Anesthesiology is seeking a BC/BE anesthesiologist with training or experience in pain management to join its 20 anesthesiologists and 17 nurse anesthetists. Pain Management Team and support specialties are in place. This practice would be split between pain management and hospital OR. Excellent compensation package. Pleasant semirural midwest community of 20,000. Please respond with cover letter, CV, and names of references to Debra K. Schuster, MD, Department of Anesthesiology, Marshfield Clinic, 1000 North Oak Avenue, Marshfield, WI 54449 or call collect at (715) 387-7179. EOE/AAM/F/H/V.

1024L

ALABAMA—ANESTHESIOLOGIST

Faculty position for clinical BC/BE anesthesiologist at University of Alabama at Birmingham, Department of Anesthesiology. Opportunities to do clinical research, variety of clinical cases including liver transplantation. Desire to participate in teaching necessary. Limited night call. Generous benefit package. Salary competitive with private practice situations. Please contact Paul N. Samuelson, MD, Professor and Chairman of Recruitment Committee, Department of Anesthesiology, University of Alabama at Birmingham, 619 South 19th Street, Birmingham, AL 35233, (205) 934-4696. An Affirmative Action/Equal Employment Opportunity Employer.

1025L/B

Albany Medical College has immediate openings for BC/BE anesthesiologists to join our staff of over 25 MDs, and over 60 CRNAs and residents, to provide team-approach anesthesia care for all types of cases. Research and teaching interest highly desirable.

We are a 660-bed, tertiary-care facility with 20 newly renovated OR suites equipped with state-of-the-art instrumentation.

Our highly competitive benefits package includes generous leave time, health and dental plan, pension and disability plan, malpractice and life insurance. Interested applicants should send CV and three references to: Philip D. Lumb, MBBS, Professor and Chairman, Albany Medical College, Department of Anesthesiology, Mail Code A-131, Albany, New York 12208.

1026LBD

PEDIATRIC ANESTHESIOLOGIST to direct Pediatric Intensive Care Unit in academic medical center. Interest in teaching and research required. Academic appointment appropriate to credentials. TJU is an Affirmation Action/Equal Opportunity Employer. Send inquiries and references to Joseph L. Seltzer, MD, Professor and Chairman, Department of Anesthesiology, Thomas Jefferson University, Philadelphia, PA 19107.

1027L/B

TENNESSEE

Expanding department requires additional anesthesiologists. Full-time positions available at levels of instructor to associate professor with emphasis on teaching, patient care, and clinical research. Prerequisites: (1) Meet Tennessee license requirements. (2) ABA diplomat or eligible for ABA examination. All subspecialties needed. Excellent opportunity for anesthesiologists who want an ideal mix of private practice with teaching and clinical research. Send curriculum vitae, bibliography, and the names and addresses of three references to John Zanella, Jr., MD, PhD, Professor and Chairman, Department of Anesthesiology, University of Tennessee, Memphis, 800 Madison Avenue, Memphis, TN 38163. The University of Tennessee is an Equal Opportunity Employer/Affirmative Action Register/Title IX/Section 504 Employer.

1028L/B

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1007L

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763I/B

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832A/L

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755I/L

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898E/L

A WEEKEND OF MOCK ORAL EXAMS
Mock orals, not lectures. We are the original course in this format. 20 hours Category I CME credit, two board-certified instructors, 12 students maximum. Tampa, January 22–24; Dallas, February 19–21; Detroit, March 12–14. ANESTHESIA EXAM REVIEW, 7128 Regents Park, Toledo, OH 43617. (419) 843-4480 or (813) 394-8780.

963J/A

CHAIRPERSON, DEPARTMENT OF ANESTHESIOLOGY, LOYOLA UNIVERSITY MEDICAL CENTER
Loyola University Medical School, Maywood, Illinois, is seeking candidates for the position of Professor and Chairperson for the Department of Anesthesiology. The department is expanding its programs in clinical care, research, and medical education. Candidates should have experience an understanding of both the clinical aspect of anesthesiology and the requirements o the Anesthesiology Residency Program The candidates must also have a distinguished record of scholarship and professional achievement, proven leadership and administrative ability.

Applications and curriculum vita should be sent to the Chairman of th Search Committee: Jack Pickleman, MD Professor and Chief Division of Genera Surgery, Department of Surgery, Loyol University Medical Center, 2160 South Firs Avenue, Maywood, IL 60153. An Affirmative Action/Equal Opportunity Employer.

1029I

THI
5 mg/mL
10 mL
VERSED®
(midazolam HCl)
midazolam 5 mg / mL
(as the hydrochloride)
For I.M. or I.V. Use
disodium edetate, with 1% benzyl alcohol
preservative and pH adjusted to approximately 3 wit
hydrochloric acid and, if necessary, sodium hydro

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THE ADVANTAGE OF CO-INDUCTION

Anesthetic Synergy

VERSED first, followed by a second anesthetic

When given first, a small dose of VERSED® (midazolam HCl/Roche) may lower the induction ED_{50} of barbiturates or narcotics up to 75%.[1-4] This synergistic effect appears to result from a mutual enhancement of binding-site affinity.[1-3] Clinically, co-induction may decrease toxicity and speed recovery.[2] VERSED can also abolish the excitatory effects and emergence phenomena associated with some induction agents,[5] and its potent amnestic effect may avoid breakthrough awareness at times when short-acting induction agents may be wearing off.

- **Allows lower doses of induction agents[1-5]**
- **A smooth induction[5]**
- **Less risk of breakthrough awareness[5]**
- **A smooth emergence[5]**

Dosing considerations

When VERSED is used before other intravenous agents for induction of anesthesia, the initial dose of each agent may be significantly reduced, at times to as low as 25% of the usual initial dose of the individual agents.

As a standard precaution, prior to I.V. administration of VERSED in any dose, oxygen and resuscitative equipment should be immediately available. VERSED should be used as an induction agent only by persons trained in anesthesiology and who are familiar with all dosing and administration guidelines. Reduce dosage in elderly or debilitated patients, in patients receiving narcotic premedication and in those with limited pulmonary reserve.

It is recommended that patients do not drive or operate hazardous machinery after receiving VERSED until the effects of the drug (*e.g.,* drowsiness) are gone or until the day after anesthesia, whichever is longer. The decision must be individualized.

Please see summary of product information on following page.

INJECTABLE

VERSED®

midazolam HCl/Roche Ⓒ

FIRST

Injectable VERSED is available in 1 mg/mL and 5 mg/mL strengths.

References: 1. Tverskoy M, et al. Midazolam-thiopental anesthetic interaction in patients. *Anesth Analg.* 1988;67:342-345. **2.** Vinik HR, Bradley EL Jr, Kissin I. Midazolam for coinduction of thiopental anesthesia in patients. *Anesthesiology.* 1990; 73(3A):A1216. **3.** Vinik HR, Bradley EL Jr, Kissin I. Midazolam-alfentanil synergism for anesthetic induction in patients. *Anesth Analg.* 1989;69:213-217. **4.** Ben-Shlomo I, et al. Midazolam acts synergistically with fentanyl for induction of anaesthesia. *Br J Anaesth.* 1990;64:45-47. **5.** White PF. Comparative evaluation of intravenous agents for rapid sequence induction — thiopental, ketamine, and midazolam. *Anesthesiology.* 1982;57:279-284.

VERSED®
midazolam HCl/Roche Ⓒ
INJECTION

Before prescribing, please consult complete product information, a summary of which follows:

> Intravenous VERSED has been associated with respiratory depression and respiratory arrest, especially when used for conscious sedation. In some cases, where this was not recognized promptly and treated effectively, death or hypoxic encephalopathy has resulted. Intravenous VERSED should be used only in hospital or ambulatory care settings, including physicians' offices, that provide for continuous monitoring of respiratory and cardiac function. Immediate availability of resuscitative drugs and equipment and personnel trained in their use should be assured. (See WARNINGS.)
>
> The initial intravenous dose for conscious sedation may be as little as 1 mg, but should not exceed 2.5 mg in a normal healthy adult. Lower doses are necessary for older (over 60 years) or debilitated patients and in patients receiving concomitant narcotics or other CNS depressants. The initial dose and all subsequent doses should never be given as a bolus; administer over at least 2 minutes and allow an additional 2 or more minutes to fully evaluate the sedative effect. The use of the 1 mg/mL formulation or dilution of the 1 mg/mL or 5 mg/mL formulation is recommended to facilitate slower injection. Consult complete product information under DOSAGE AND ADMINISTRATION for complete dosing information.

CONTRAINDICATIONS: Patients with known hypersensitivity to the drug. Benzodiazepines are contraindicated in patients with acute narrow angle glaucoma; may be used in open angle glaucoma only if patients are receiving appropriate therapy.

Not intended for intrathecal or epidural administration due to the presence of the preservative benzyl alcohol.

WARNINGS: Never use without individualization of dosage. Prior to IV use in any dose, ensure immediate availability of oxygen, resuscitative equipment and skilled personnel for maintenance of a patent airway and support of ventilation. Continuously monitor for early signs of underventilation or apnea, which can lead to hypoxia/cardiac arrest unless effective countermeasures are taken immediately. Vital signs should continue to be monitored during the recovery period.

Because IV VERSED depresses respiration, and opioid agonists and other sedatives can add to this depression, it should be administered as an induction agent only by a person trained in general anesthesia and should be used for conscious sedation only in the presence of personnel skilled in early detection of underventilation, maintaining a patent airway and supporting ventilation. **For conscious sedation, do not administer IV by rapid or single bolus.** Serious cardiorespiratory adverse events have occurred. These have included respiratory depression, apnea, respiratory arrest and/or cardiac arrest, sometimes resulting in death. There have been rare reports of hypotensive episodes requiring treatment during or after diagnostic or surgical manipulations in patients who have received VERSED. Hypotension occurred more frequently in the conscious sedation studies in patients premedicated with narcotic.

Reactions such as agitation, involuntary movements, hyperactivity and combativeness have been reported. These may be due to inadequate or excessive dosing or improper administration; however, the possibility of cerebral hypoxia or true paradoxical reactions should be considered. Should these reactions occur, response to each dose of VERSED and all other drugs should be evaluated before proceeding.

Concomitant use of barbiturates, alcohol or other CNS depressants may increase the risk of underventilation or apnea and may contribute to profound and/or prolonged drug effect. Narcotic premedication also depresses the ventilatory response to carbon dioxide stimulation.

Higher risk surgical, elderly or debilitated patients require lower dosages for induction of anesthesia, premedicated or not. Patients with chronic obstructive pulmonary disease are unusually sensitive to the respiratory depressant effect of VERSED. Patients with chronic renal failure and patients with congestive heart failure eliminate midazolam more slowly. Because elderly patients frequently have inefficient function of one or more organ systems, and because dosage requirements have been shown to decrease with age, reduce initial dosage and consider possibility of a profound and/or prolonged effect.

Do not administer in shock, coma, acute alcohol intoxication with depression of vital signs. Particular care should be exercised in the use of IV VERSED in patients with uncompensated acute illnesses, such as severe fluid or electrolyte disturbances.

Guard against unintended intra-arterial injection; hazards in humans unknown. Avoid extravasation.

VERSED should only be administered IM or IV. Safety and efficacy of other routes of administration are not established.

Gross tests of recovery from the effects of VERSED cannot alone predict reaction time under stress. This drug is never used alone during anesthesia, and the contribution of other perioperative drugs and events can vary. The decision as to when patients may engage in activities requiring mental alertness must be individualized; it is recommended that no patient should operate hazardous machinery or a motor vehicle until the effects of the drug, such as drowsiness, have subsided or until the day after anesthesia, whichever is longer.

Usage in Pregnancy: An increased risk of congenital malformations associated with the use of benzodiazepines (diazepam and chlordiazepoxide) has been suggested in several studies. If VERSED is used during pregnancy, apprise the patient of the potential hazard to the fetus.

PRECAUTIONS: *General:* Decrease intravenous doses in elderly and debilitated patients. These patients will also probably take longer to recover completely after VERSED for induction of anesthesia.

VERSED does not protect against increased intracranial pressure or against the heart rate rise and/or blood pressure rise associated with endotracheal intubation under light general anesthesia.

Information for patients: Communicate the following information and instructions to the patient when appropriate: 1. Inform your physician about any alcohol consumption and medicine you are now taking, including nonprescription drugs. Alcohol has an increased effect when consumed with benzodiazepines; therefore, caution should be exercised regarding simultaneous ingestion of alcohol and benzodiazepines. 2. Inform your physician if you are pregnant or are planning to become pregnant. 3. Inform your physician if you are nursing.

VERSED® (midazolam HCl/Roche)

Drug interactions: The sedative effect of IV VERSED is accentuated by premedication, particularly narcotics (*e.g.*, morphine, meperidine, fentanyl) and also secobarbital and Innovar (fentanyl and droperidol). Consequently, adjust the dosage according to the type and amount of premedication.

A moderate reduction in induction dosage requirements of thiopental (about 15%) has been noted following use of IM VERSED for premedication.

IV administration of VERSED decreases the minimum alveolar concentration (MAC) of halothane required for general anesthesia. This decrease correlates with the dose of VERSED administered.

Although the possibility of minor interactive effects has not been fully studied, VERSED and pancuronium have been used together in patients without noting clinically significant changes in dosage, onset or duration. VERSED does not protect against the characteristic circulatory changes noted after administration of succinylcholine or pancuronium, or against the increased intracranial pressure noted following administration of succinylcholine. VERSED does not cause a clinically significant change in dosage, onset or duration of a single intubating dose of succinylcholine.

No significant adverse interactions with commonly used premedications or drugs used during anesthesia and surgery (including atropine, scopolamine, glycopyrrolate, diazepam, hydroxyzine, d-tubocurarine, succinylcholine and nondepolarizing muscle relaxants) or topical local anesthetics (including lidocaine, dyclonine HCl and Cetacaine) have been observed.

Clearance of midazolam and certain other benzodiazepines may be delayed with concomitant administration of cimetidine (but not ranitidine). Clinical significance of this interaction is unclear.

Drug/laboratory test interactions: Midazolam has not been shown to interfere with clinical laboratory test results.

Carcinogenesis, mutagenesis, impairment of fertility: Midazolam maleate was administered to mice and rats for two years. At the highest dose (80 mg/kg/day) female mice had a marked increase in incidence of hepatic tumors and male rats had a small but significant increase in benign thyroid follicular cell tumors. These tumors were found after chronic use, whereas human use will ordinarily be of single or several doses.

Midazolam did not have mutagenic activity in tests that were conducted.

A reproduction study in rats did not show any impairment of fertility at up to ten times the human IV dose.

Pregnancy: Teratogenic effects: Pregnancy Category D. See WARNINGS section. Midazolam maleate injectable, at 5 and 10 times the human dose, did not show evidence of teratogenicity in rabbits and rats.

Labor and delivery: Use in obstetrics has not been evaluated. Because midazolam is transferred transplacentally and because other benzodiazepines given in the last weeks of pregnancy have resulted in neonatal CNS depression, VERSED is not recommended for obstetrical use.

Nursing mothers: Excreted in human milk. Not recommended for use in nursing mothers.

Pediatric use: Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS: See WARNINGS concerning serious cardiorespiratory events and possible paradoxical reactions. Fluctuations in vital signs following parenteral administration were the most frequently seen findings and included decreased tidal volume and/or respiratory rate decrease (23.3% of patients following IV and 10.8% of patients following IM administration) and apnea (15.4% of patients following IV administration), as well as variations in blood pressure and pulse rate.

Following IM injection: headache (1.3%); local effects at IM site: pain (3.7%), induration (0.5%), redness (0.5%), muscle stiffness (0.3%).

IM administration to elderly and/or high-risk surgical patients has been associated with rare reports of death under circumstances compatible with cardiorespiratory depression. In most of these cases, patients also received other CNS depressants capable of depressing respiration, especially narcotics.

Following IV administration: hiccoughs (3.9%), nausea (2.8%), vomiting (2.6%), coughing (1.3%), "oversedation" (1.6%), headache (1.5%), drowsiness (1.2%); local effects at the IV site: tenderness (5.6%), pain during injection (5.0%), redness (2.6%), induration (1.7%), phlebitis (0.4%). Other effects (<1%) mainly following IV administration: *Respiratory:* Laryngospasm, bronchospasm, dyspnea, hyperventilation, wheezing, shallow respirations, airway obstruction, tachypnea. *Cardiovascular:* Bigeminy, premature ventricular contractions, vasovagal episode, bradycardia, tachycardia, nodal rhythm. *Gastrointestinal:* Acid taste, excessive salivation, retching. *CNS/Neuromuscular:* Retrograde amnesia, euphoria, hallucination, confusion, argumentativeness, nervousness, anxiety, grogginess, restlessness, emergence delirium or agitation, prolonged emergence from anesthesia, dreaming during emergence, sleep disturbance, insomnia, nightmares, athetoid movements, seizure-like activity, ataxia, dizziness, dysphoria, slurred speech, dysphonia, paresthesia. *Special Sense:* Blurred vision, diplopia, nystagmus, pinpoint pupils, cyclic movements of eyelids, visual disturbance, difficulty focusing eyes, ears blocked, loss of balance, lightheadedness. *Integumentary:* Hive-like elevation at injection site, swelling or feeling of burning, warmth or coldness at injection site. *Hypersensitivity:* Allergic reactions, including anaphylactoid reactions, hives, rash, pruritus. *Miscellaneous:* Yawning, lethargy, chills, weakness, toothache, faint feeling, hematoma.

Drug Abuse and Dependence: Available data concerning the drug abuse and dependence potential of midazolam suggest that its abuse potential is at least equivalent to that of diazepam.

OVERDOSAGE: Manifestations would resemble those observed with other benzodiazepines (*e.g.*, sedation, somnolence, confusion, impaired coordination, diminished reflexes, coma, untoward effects on vital signs). No specific organ toxicity would be expected.

DOSAGE AND ADMINISTRATION: VERSED is a potent sedative agent which requires slow administration and individualization of dosage. Clinical experience has shown VERSED to be 3 to 4 times as potent per mg as diazepam. BECAUSE SERIOUS AND LIFE-THREATENING CARDIORESPIRATORY ADVERSE EVENTS HAVE BEEN REPORTED, PROVISION FOR MONITORING, DETECTION AND CORRECTION OF THESE REACTIONS MUST BE MADE FOR EVERY PATIENT TO WHOM VERSED INJECTION IS ADMINISTERED, REGARDLESS OF AGE OR HEALTH STATUS. Excess doses or rapid or single bolus intravenous administration may result in respiratory depression and/or arrest. (See WARNINGS.) Prior to use refer to the DOSAGE AND ADMINISTRATION section in the complete product information.

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Alfenta®

lfentanil HCl) Injection CII

ore prescribing, please consult complete prescribing information, of which the following is rief summary.

UTION: Federal Law Prohibits Dispensing Without Prescription
SCRIPTION: ALFENTA is a sterile, non-pyrogenic, preservative free aqueous solution containing alfentanil drochloride equivalent to 500 µg per ml of alfentanil base for intravenous injection. The solution, which contains lium chloride for isotonicity, has a pH range of 4.0-6.0.
NTRAINDICATIONS: ALFENTA (alfentanil hydrochloride) is contraindicated in patients with known hyper- nsitivity to the drug.
ARNINGS: ALFENTA SHOULD BE ADMINISTERED ONLY BY PERSONS SPECIFICALLY TRAINED IN THE USE OF TRAVENOUS AND GENERAL ANESTHETIC AGENTS AND IN THE MANAGEMENT OF RESPIRATORY EFFECTS OF TENT OPIOIDS. AN OPIOID ANTAGONIST, RESUSCITATIVE AND INTUBATION EQUIPMENT AND OXYGEN SHOULD E READILY AVAILABLE. BECAUSE OF THE POSSIBILITY OF DELAYED RESPIRATORY DEPRESSION, MONITORING F THE PATIENT MUST CONTINUE WELL AFTER SURGERY. ALFENTA (alfentanil hydrochloride) administered in itial dosages up to 20 µg/kg may cause skeletal muscle rigidity, particularly of the truncal muscles. The incidence d severity of muscle rigidity is usually dose-related. Administration of ALFENTA at anesthetic induction dosages bove 130 µg/kg) will consistently produce muscular rigidity with an immediate onset. The onset of muscular gidity occurs earlier than with other opioids. ALFENTA may produce muscular rigidity that involves all skeletal uscles, including those of the neck and extremities. The incidence may be reduced by: 1) routine methods of dministration of neuromuscular blocking agents for balanced opioid anesthesia; 2) administration of up to ¼ of the l paralyzing dose of a neuromuscular blocking agent just prior to administration of ALFENTA at dosages up to g/kg; following loss of consciousness, a full paralyzing dose of a neuromuscular blocking agent should be nistered; or 3) simultaneous administration of ALFENTA and a full paralyzing dose of a neuromuscular blocking t when ALFENTA is used in rapidly administered anesthetic dosages (above 130 µg/kg). The neuromuscular king agent used should be appropriate for the patient's cardiovascular status. Adequate facilities should be able for postoperative monitoring and ventilation of patients administered ALFENTA. It is essential that these ties be fully equipped to handle all degrees of respiratory depression.
ECAUTIONS: DELAYED RESPIRATORY DEPRESSION, RESPIRATORY ARREST, BRADYCARDIA, ASYSTOLE, RHYTHMIAS AND HYPOTENSION HAVE ALSO BEEN REPORTED. THEREFORE, VITAL SIGNS MUST BE MONITORED ONTINUOUSLY.
eneral: The initial dose of ALFENTA (alfentanil hydrochloride) should be appropriately reduced in elderly and ebilitated patients. The effect of the initial dose should be considered in determining supplemental doses. In obese patients (more than 20% above ideal total body weight), the dosage of ALFENTA should be determined on the basis of lean body weight. In one clinical trial, the dose of ALFENTA required to produce anesthesia, as determined by appearance of delta waves in EEG, was 40% lower in geriatric patients than that needed in healthy young patients. n patients with compromised liver function and in geriatric patients, the plasma clearance of ALFENTA may be reduced and postoperative recovery may be prolonged. Induction doses of ALFENTA should be administered slowly (over three minutes). Administration may produce loss of vascular tone and hypotension. Consideration should be given to fluid replacement prior to induction. Diazepam administered immediately prior to or in conjunction with high doses of ALFENTA may produce vasodilation, hypotension and result in delayed recovery. Bradycardia produced by ALFENTA may be treated with atropine. Severe bradycardia and asystole have been successfully treated with atropine and conventional resuscitative methods. The hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required should be considered in the selection of a neuromuscular blocking agent. Following an anesthetic induction dose of ALFENTA, requirements for volatile inhalation anesthetics or ALFENTA infusion are reduced by 30 to 50% for the first hour of maintenance. Administration of ALFENTA infusion should be discontinued at leas 10-15 minutes prior to the end of surgery. Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists such as naloxone. Because the duration of respiratory depression produced by ALFENTA may last longer than the duration of the opioid antagonist action, appropriate surveillance should be maintained. As with all potent opioids, profound analgesia is accompanied by respiratory depression and diminished sensitivity to CO_2 stimulation which may persist into or recur in the postoperative period. Intraoperative hyperventilation may further alter postoperative response to CO_2. Appropriate postoperative monitoring should be employed, particularly after infusions and large doses of ALFENTA, to ensure that adequate spontaneous breathing is established and maintained in the absence of stimulation prior to discharging the patient from the recovery area.
Head Injuries: ALFENTA may obscure the clinical course of patients with head injuries.
Impaired Respiration: ALFENTA should be used with caution in patients with pulmonary disease, decreased respiratory reserve or potentially compromised respiration. In such patients, opioids may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration.
Impaired Hepatic or Renal Function: In patients with liver or kidney dysfunction, ALFENTA should be administered with caution due to the importance of these organs in the metabolism and excretion of ALFENTA.
Drug Interactions: Both the magnitude and duration of central nervous system and cardiovascular effects may be enhanced when ALFENTA is administered in combination with other CNS depressants such as barbiturates, tranquilizers, opioids, or inhalation general anesthetics. Postoperative respiratory depression may be enhanced or prolonged by these agents. In such cases of combined treatment, the dose of one or both agents should be reduced. Limited clinical experience indicates that requirements for volatile inhalation anesthetics are reduced by 30 to 50% for the first sixty (60) minutes following ALFENTA induction. The concomitant use of erythromycin with ALFENTA can significantly inhibit ALFENTA clearance and may increase the risk of prolonged or delayed respiratory depression. Perioperative administration of drugs affecting hepatic blood flow or enzyme function may reduce plasma clearance and prolong recovery.
Carcinogenesis, Mutagenesis and Impairment of Fertility: No long-term animal studies of ALFENTA have been performed to evaluate carcinogenic potential. The micronucleus test in female rats and the dominant lethal test in female and male mice revealed that single intravenous doses of ALFENTA as high as 20 mg/kg (approximately 40 times the upper human dose) produced no structural chromosome mutations or induction of dominant lethal mutations. The Ames *Salmonella typhimurium* metabolic activating test also revealed no mutagenic activity.
Pregnancy Category C: ALFENTA has been shown to have an embryocidal effect in rats and rabbits when given in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects could have been due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug. No evidence of teratogenic effects has been observed after administration of ALFENTA in rats or rabbits. There are no adequate and well-controlled studies in pregnant women. ALFENTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Labor and Delivery: There are insufficient data to support the use of ALFENTA in labor and delivery. Placental transfer of the drug has been reported; therefore, use in labor and delivery is not recommended.
Nursing Mothers: In one study of nine women undergoing post-partum tubal ligation, significant levels of ALFENTA were detected in colostrum four hours after administration of 60 µg/kg of ALFENTA, with no detectable levels present after 28 hours. Caution should be exercised when ALFENTA is administered to a nursing woman.
Pediatric Use: Adequate data to support the use of ALFENTA in children under 12 years of age are not presently available.
ADVERSE REACTIONS: The most common adverse reactions, respiratory depression and skeletal muscle rigidity, are extensions of known pharmacological effects of opioids. See CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS on the management of respiratory depression and skeletal muscle rigidity. Delayed respiratory depression, respiratory arrest, bradycardia, asystole, arrhythmias and hypotension have also been reported. The reported incidences of adverse reactions listed in the following table are derived from controlled and open clinical trials involving 1183 patients, of whom 785 received ALFENTA. The controlled trials involved treatment comparisons with fentanyl, thiopental sodium, enflurane, saline placebo and halothane. Incidences are based on disturbing and nondisturbing adverse reactions reported. The comparative incidence of certain side effects is influenced by the type of use, e.g., chest wall rigidity has a higher reported incidence in clinical trials of alfentanil induction, and by the type of surgery, e.g., nausea and vomiting have a higher incidence in patients undergoing gynecologic surgery.

Percent	ALFENTA (N = 785)	Fentanyl (N = 243)	Thiopental Sodium (N = 66)	Enflurane (N = 55)	Halothane (N = 18)	Saline Placebo* (N = 18)
Gastrointestinal						
Nausea	28	44	14	5	0	22
Vomiting	18	31	11	9	13	17
Cardiovascular						
Bradycardia	14	7	8	0	0	0
Tachycardia	12	12	39	36	31	11
Hypotension	10	8	7	7	0	0
Hypertension	18	13	30	20	6	0
Arrhythmia	2	2	5	4	6	0
Musculoskeletal						
Chest Wall Rigidity	17	12	0	0	0	0
Skeletal Muscle Movements	6	2	6	2	0	0
Respiratory						
Apnea	7	0	0	0	0	0
Postoperative Respiratory Depression	2	2	0	0	0	0
CNS						
Dizziness	3	5	0	0	0	0
Sleepiness/ Postoperative Sedation	2	8	2	0	0	6
Blurred Vision	2	2	0	0	0	0

*From two clinical trials, one involving supplemented balanced barbiturate / nitrous oxide anesthesia and one in healthy volunteers who did not undergo surgery.

In addition, other adverse reactions less frequently reported (1% or less) were: Laryngospasm, bronchospasm, postoperative confusion, headache, shivering, postoperative euphoria, hypercarbia, pain on injection, urticaria, and itching. Some degree of skeletal muscle rigidity should be expected with induction doses of ALFENTA.
DRUG ABUSE AND DEPENDENCE: ALFENTA (alfentanil hydrochloride) is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and therefore has the potential for being abused.
OVERDOSAGE: Overdosage would be manifested by extension of the pharmacological actions of ALFENTA (alfentanil hydrochloride) (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. No experience of overdosage with ALFENTA was reported during clinical trials. The intravenous LD_{50} of ALFENTA is 43.0-50.9 mg/kg in rats, 72.2-73.6 mg/kg in mice, 71.8-81.9 mg/kg in guinea pigs and 59.5-87.5 mg/kg in dogs. Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression. The duration of respiratory depression following overdosage with ALFENTA may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist should not preclude immediate establishment of a patent airway, administration of oxygen, and assisted or controlled ventilation as indicated for hypoventilation or apnea. If respiratory depression is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled ventilation. Intravenous fluids and vasoactive agents may be required to manage hemodynamic instability.
DOSAGE AND ADMINISTRATION: The dosage of ALFENTA (alfentanil hydrochloride) should be individualized in each patient according to body weight, physical status, underlying pathological condition, use of other drugs, and type and duration of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of ALFENTA should be determined on the basis of lean body weight. The dose of ALFENTA should be reduced in elderly or debilitated patients (see PRECAUTIONS). Vital signs should be monitored routinely. Protect from light. Store at room temperature 15°-30° C (59°-86° F).

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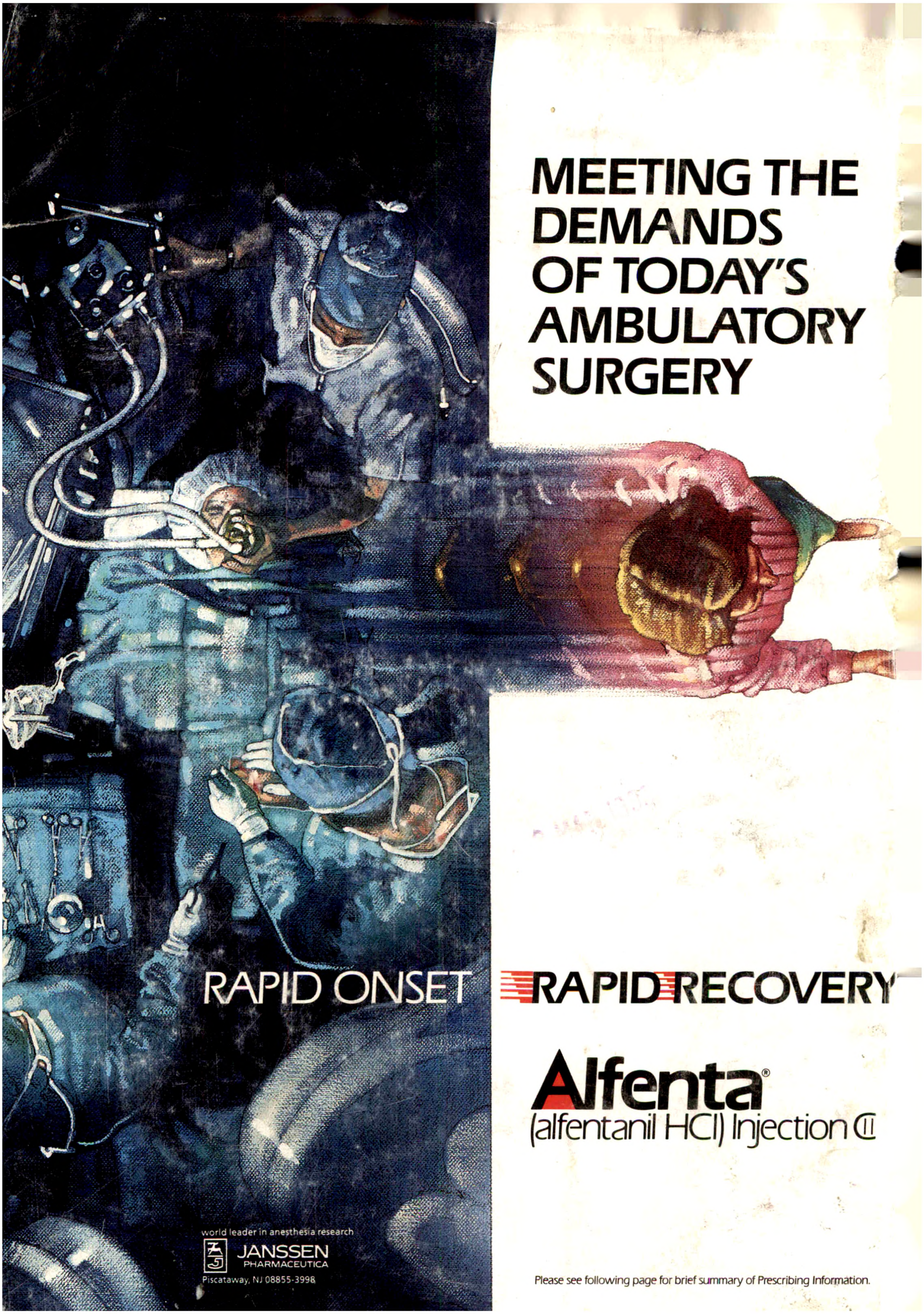

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